Specificity of Insulin Degradation Reaction

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In a previous publication,[1] inferential evidence was presented indicating that the distribution of the radioactivity of injected insulin labeled with radioactive iodine (I^{131}) is probably representative of the distribution of unlabeled insulin. In the present report, further evidence of the specificity of insulin-I^{131} is presented in the demonstration that the degradation of a trace amount of insulin-I^{131} is competitively lessened by a load of either labeled or nonlabeled insulin, and not by other proteins of similar size. The distribution and degradation of ribonuclease, a nonhormonal protein of comparable molecular weight to insulin and labeled with I^{131}, is, however, shown to be very similar to that of insulin-I^{131}.

METHODS

The basic technics have been described previously.[1] Sprague-Dawley rats were prepared for use by replacing their food and water with 10 per cent dextrose in 0.9 per cent saline the night before use and withdrawing this one to two hours before the experiment. The labeled protein (in various preparations to be described below) was dissolved in 0.067 *M.* phosphate buffer,‡ *p*H 7.5, and injected into the tail vein. At a given time thereafter, the animal was sacrificed and the liver, kidney, muscle, and blood were removed. In some instances plasma was separated. Since the radioactivity of the I^{131}-labeled proteins was essentially completely precipitable with trichloracetic acid (TCA), degradation of the labeled protein was estimated by dividing the radioactivity of the tissues into a supernatant and a precipitate fraction by means of TCA precipitation and washing, as described previously.[1] The appearance of nonprecipitable radioactivity was taken to represent degradation. In some instances the concentration of radioactivity was expressed as [T]/[B], a value calculated by multiplying the tissue fraction radioactivity concentration, (the percentage of the total I^{131} dose, per gram of tissue) by the body weight/100, so that values greater than 1 represented concentrations of radioactivity greater than that in the body as a whole.

EXPERIMENTS AND RESULTS

1. Influence of an Insulin Load on the Distribution and Degradation of Insulin-I^{131}

One group of rats received 0.4 ml. (200 units) of concentrated crystalline insulin intravenously immediately before 0.5 ml. (0.5 units) of insulin-I^{131}* was similarly administered. A control group received insulin-I^{131} only. Tissue radioactivity was fractionated and assayed fifteen minutes later, as described in methods above.

The results are shown in figure 1. Relative distribution of total radioactivity in the various organs was not greatly altered. Precipitable radioactivity was increased in liver and blood and decreased in kidney in the loaded animals. The outstanding finding was a significant reduction in the supernatant fraction of all tissues in the animals which received a load of nonlabeled insulin. The apparent interpretation of this finding is that the degradation of insulin-I^{131} was competitively depressed by nonlabeled insulin.

2. Depression of Insulin-I^{131} Degradation by Labeled and Nonlabeled Insulin

Even though the above animals showed little adverse reaction during the short time interval they were permitted to live, the insulin load used was relatively enormous, and a second experiment, using smaller but increasing increments in dosage, was performed. Since it was felt to be probable that the degradation of the insulin-I^{131} substrate was diminished because of competition for the degradation system by the unlabeled insulin, the effects of adding increasing amounts of unlabeled insulin to a trace amount of labeled insulin were compared with the effects on degradation found when

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‡This is referred to simply as buffer in the remainder of the paper.

*Crystalline insulin was kindly supplied by Eli Lilly and Company. It was iodinated with I^{131} by the Abbott Laboratories at Oak Ridge. The properties of insulin-I^{131} have been presented previously.[1]

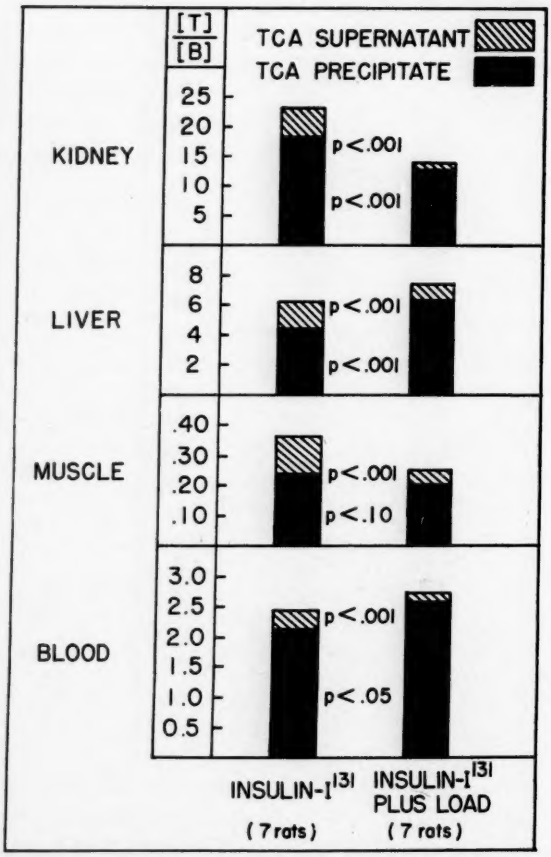

FIG. 1. Comparison of the concentrations, [T]/[B], of radioactivity in tissue fractions fifteen minutes after intravenous insulin-I^{131} was given to control rats and to rats which, immediately before the insulin-I^{131}, were given a load of 200 units of nonlabeled insulin intravenously. Tissue radioactivity was divided into a supernatant and a precipitate fraction by means of trichloracetic acid (TCA) precipitation. The figures between the columns are p values of the differences between the fractions in the two adjacent groups.

increasing loads of insulin-I^{131} alone were used. The experiment was therefore designed using a technic comparable to that of substrate competition, chiefly to see if the degradation system distinguished between labeled and unlabeled insulin in vivo.

Eleven female rats, weighing between 206 and 242 gm., were given doses of insulin-I^{131} ranging from 2 to 222 *ug*. Twelve female rats, weighing between 195 and 240 gm., were given 2 *ug*. of insulin-I^{131} in solution with doses of nonlabeled insulin varying from 1 to 122 *ug*. so that the total dose varied from 3 to 124 *ug*. of insulin. The nonlabeled insulin used was the same lot of crystalline insulin,* 27 units per mg., from which the insulin-I^{131} was prepared. Each rat received a particular dose of either insulin-I^{131} or a particular combination of insulin-I^{131} with nonlabeled insulin, each dose being dissolved in 1 ml. of buffer. The animals were sacrificed fifteen minutes later. One aliquot of blood was immediately precipitated in TCA. Plasma was similarly precipitated after it was separated from a second aliquot of blood.

The percentage of the total radioactivity per milliliter of blood or plasma that was in the TCA supernatant fraction is plotted against the total dose of insulin (labeled and nonlabeled) injected, in figures 2 and 3, respectively.

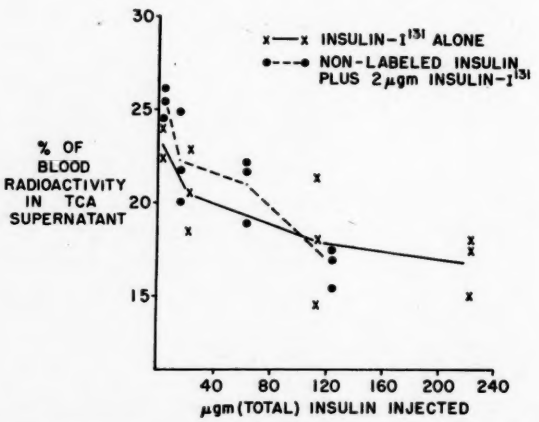

FIG. 2. Rats were injected intravenously with varying doses of insulin-I^{131}. Twelve received 2 ug. of insulin-I^{131} and varying doses of nonlabeled insulin in addition. All rats were sacrificed fifteen minutes later, and an aliquot of blood was precipitated with trichloracetic acid (TCA). The percentage of the blood radioactivity that was in the TCA supernatant is plotted against the total ug. of insulin (labeled and nonlabeled) injected. Each point represents one rat, and the lines indicate the mean.

As the dose was increased the percentage of radioactivity in the supernatant fraction was seen to fall. This was seen to be true, and to the same extent, whether the dose increase was made up of labeled or nonlabeled insulin. Either substrate was able to "load" the system and depress degradation, and the presence of an I^{131} label appeared to make no difference.

3. Effects of Other Proteins on the Degradation of Insulin-I^{131}

Proteins of molecular weights similar to insulin were

*Kindly supplied by Eli Lilly and Company.

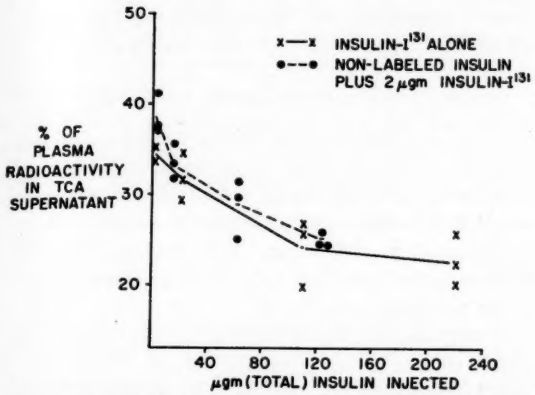

FIG. 3. Data obtained in similar fashion to that of figure 2 except that plasma was used instead of blood. Note that the curves are essentially superimposable — the effect of "load" on degradation was the same whether labeled or nonlabeled insulin was used.

tested to see if they competed in or inhibited the degradation of insulin-I^{131}. Using a technic similar to that in the preceding experiment, insulin-I^{131} was injected into rats in combinations with these other proteins, and blood radioactivity was determined fifteen minutes later. The addition of 150 *ug.* of corticotropin,* 150 *ug.* of ribonuclease, or 200 *ug.* of *a* lactalbumin to 4 *ug.* of insulin-I^{131} was found to have no effect on the percentage of radioactivity that appeared in the supernatant fraction of blood and plasma, it being the same as when the 4 *ug.* of insulin-I^{131} was injected alone. As noted before, however, the addition of 150 *ug.* of insulin to the insulin-I^{131} significantly diminished the percentage of radioactivity that appeared in the supernatant.

4. Distribution and Degradation of Ribonuclease-I^{131}

Ribonuclease was obtained from Montgomery Biochemicals and labeled by the Abbott Laboratories in North Chicago using I^{131} in the technique by which they label insulin. After dialysis overnight against buffer its radioactivity was found to be 98.2 per cent precipitable by TCA. Approximately 0.2 mg., 10 *uc.*, of dialyzed ribonuclease-I^{131} dissolved in 0.5 ml. of buffer was then given intravenously to each of fifteen female rats, weighing between 152 and 193 gm. Five rats were sacrificed at each of three time periods after the injection — five, thirty, and sixty minutes. The concentrations of radioactivity in the various tissue fractions are plotted against time in figure 4.

Blood and muscle levels were virtually identical to those found previously with insulin-I^{131}. Renal concentrations were very high, in fact several fold higher than those with insulin-I^{131}, and hepatic concentrations were somewhat lower. The renal concentration was found to be high in cortex and low in medulla. In all tissues the supernatant fraction of radioactivity increased with time, while the precipitable fraction rapidly fell. Similar experiments were done in male rats with essentially the same findings.

*The corticotropin (HP Acthar) was kindly supplied by Armour Laboratories.

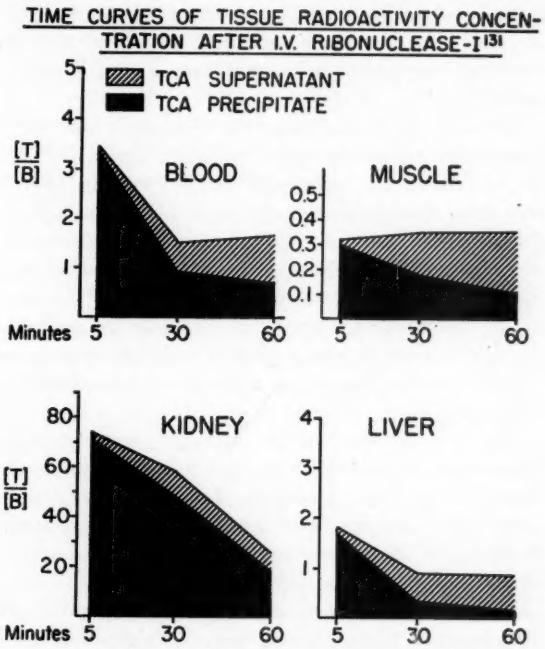

FIG. 4. The distribution of radioactivity in the TCA precipitate and supernatant fractions of tissues at various times after the intravenous injection of I^{131}-labeled ribonuclease into rats. The concentration of radioactivity is expressed as [T]/[B], the ratio of the concentration in a given tissue fraction to that initially in the body as a whole. A value of [T]/[B] greater than 1 indicates that the concentration of radioactivity exceeds that of the body as a whole.

DISCUSSION

The degradation of insulin-I^{131} by liver extracts in vitro, as measured by the loss of TCA precipitability, has been shown to proceed with essentially the same dynamics as the process of inactivation[2-4] of nonlabeled insulin, perhaps because these processes represent cause and effect. The dynamics have been found to be those of an enzyme system.[2-4] In experiment 1 of this report it is shown that excess crystalline insulin depresses the rate of degradation of insulin-I^{131} in vivo. In experiment 2 it is shown that this depression increases as the dose is increased, and

is the same whether labeled or nonlabeled insulin is used as excess substrate. These data are consistent with the view that the process of degradation in vivo is also enzymatic.

The substrate competition data demonstrate that the degradation system does not distinguish between I^{131}-labeled insulin and nonlabeled insulin. Further, since nonlabeled insulin can compete for or inhibit the degradation system it is most unlikely that the measure of degradation, that is, the appearance of radioactivity in the TCA supernatant, represents cleavage of free I^{131} from the protein molecule. This is consistent with the in vitro findings of others[2] in which nonprotein nitrogen appeared concurrently with supernatant radioactivity in insulin-I^{131} degradation.

The fact demonstrated in experiment 3 — that the degradation of insulin-I^{131} is not depressed by proteins other than insulin — is evidence of the specificity of this system, and adds weight to the view that measurement of insulin-I^{131} degradation provides information of value in the study of insulin metabolism.

That the type of distribution and degradation found with insulin-I^{131} is not unique, however, is shown by the ribonuclease data. Early in our work a very high renal concentration of radioactivity was noted in rat kidney shortly after the injection of insulin-I^{131}. Sonenberg[5] had found similar high renal concentrations of radioactivity after giving corticotropin-I^{131}, although more active preparations showed lesser concentrations. We found no comparable renal concentration with I^{131}-labeled human serum albumin,[1] and were interested in the possibility that the molecular weight of the protein might be a factor relating to the distribution pattern, the two hormones noted above both being quite small. Accordingly we have studied the distribution and degradation of an I^{131}-labeled, nonhormonal protein, of small molecular weight, ribonuclease-I^{131}.

In experiment 4, ribonuclease-I^{131} was found to have a distribution very similar to that of insulin-I^{131}. This is evidence that molecular size may have a bearing on the distribution pattern of these substances. Since ribonuclease is not a hormone, the similarity of its distribution to that of insulin-I^{131} and corticotropin-I^{131} makes it unlikely that the distributions of the latter two are related solely to their hormonal character. It is not surprising, then, that ribonuclease-I^{131}, like insulin-I^{131}, is rapidly degraded in the body. This suggests that degradation of insulin-I^{131} is probably not dependent on its hormonal character or action. It is, however, compatible with the previously expressed postulate that the degradation represents inactivation.[1]

SUMMARY

1. The degradation of insulin labeled with radioactive iodine (I^{131}) in vivo as measured by the appearance of trichloracetic acid supernatant radioactivity in tissues in rats, is depressed by excess nonlabeled insulin.

2. Degradation of insulin-I^{131} is depressed, and to the same extent, with increasing loads of either insulin-I^{131} or nonlabeled insulin.

3. Degradation of insulin-I^{131} is not depressed by the several proteins tested, other than insulin.

It is concluded that the degradation system has a certain degree of specificity, does not distinguish between labeled and nonlabeled insulin, and that, therefore, measurement of the degradation of insulin-I^{131} probably is representative of the degradation of nonlabeled insulin.

4. That the type of distribution and degradation pattern found with insulin-I^{131} is not a property solely of hormones, is shown in the demonstration that a very similar pattern is found with I^{131}-labeled ribonuclease.

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SUMMARIO IN INTERLINGUA

Specificitate del Degradation de Insulina

1. In experimentos con rattos il esseva demonstrate que le injection de un excesso de nonetiquettate insulina deprime le degradation de dosages previemente administrate de insulina etiquettate con iodo radioactive (I^{131}) in tanto que ille degradation es mesurabile per le apparition de supernatante radioactivitate de acido trichloracetic in le texitos del animales.

2. Le degradation de insulina a I^{131} es deprimite al mesme grado per augmentate cargas de insulina o eti-

quettate con I^{131} o nonetiquettate.

3. Le degradation de insulina a I^{131} non es deprimite per le serie de altere proteinas examinate in iste reaction.

Nos conclude que le systema de degradation possede un certe grado de specificitate, que illo non distingue inter insulina etiquettate e nonetiquettate e que ergo le mesuration del degradation de insulina a I^{131} es probabilemente un mesuration indirecte del degradation de insulina nonetiquettate.

4. Le typo de distribution e degradation observate con insulina a I^{131} non es un proprietate exclusive del hormones. Isto es demonstrate per le facto que un simile typo de distribution e degradation es observate con ribonuclease etiquettate a I^{131}.

Classification of Insulin Reactions

It is suggested that the symptoms commonly seen in insulin reactions be divided into two main types, (1) "adrenalin-like" and (2) "central-nervous-system-type," regardless of whether or not both sets of symptoms may be produced by a single mechanism. This separation of symptoms is not only logical but also permits a clearer visualization of what is occurring in any particular reaction. Even more important is the increased ability to detect atypical reactions and the better appreciation of the danger of the apparently mild central nervous system reactions that have become so common.

"Adrenalin-like" Reaction: The symptoms of the "adrenalin-like" reactions are thought to result from an excess of circulating epinephrine. The entire mechanism by which the adrenal medulla is stimulated to secrete epinephrine following a fall in blood sugar remains unknown. In general, reactions of this type are associated with rapid falls in blood sugar, and for this reason they most commonly follow the injection of fast-acting insulin, sudden and excessive physical activity, or the missing of a meal combined with ordinary physical activity. Occasionally, mild symptoms of this type may be observed in persons with a rapid fall in blood sugar even though a hypoglycemic level is not reached. Since early experience with insulin was limited to the fast-acting regular insulin, almost all hypoglycemic states due to insulin reactions were associated with symptoms of the "adrenalin-like" type. For this reason there is little wonder that it was this group of symptoms that became synonymous with the term hypoglycemia, and it is equally not surprising that insulin reactions in which the "adrenalin-like" symptoms are minimal or absent are still overlooked or misinterpreted.

Central-Nervous-System-Type Reactions: The "central-nervous-system-type" reactions are the result of reduced activity of the central nervous system. The exact mechanics of this situation remain poorly understood; however, it would appear that if the nerve cells were deprived of their single source of energy for any considerable period of time serious dysfunction would be bound to result. Should this deprivation continue for a prolonged period, irreparable damage would be expected to occur. Such are the clinical facts. It is also not only possible but probable that during periods of low cerebral activity, as during sleep or relative inactivity, the requirements of the central nervous system for glucose are greatly reduced. For this reason a slowly developing hypoglycemia could remain obscure. The slowly developing hypoglycemia that is produced by the slow-acting insulins does not cause an increase in circulating epinephrine. The absence of the epinephrine explains the absence of the "adrenalin-like" symptoms as well as the failure of the blood sugar to rise and correct the hypoglycemic state. Finally, as a result of a continuing deficiency of blood glucose, there is inadequate cerebral function and the appearance of the "central-nervous-system-type" of insulin reaction.

Mixed Reactions: Frequently both the "adrenalin-like" and "central-nervous-system-type" symptoms occur in a single reaction, although one or the other generally predominates. A reaction of this type may be visualized as occurring in several ways. In spite of an increase in circulating epinephrine, the blood sugar may fail to rise because of inadequate glycogen stores or an overwhelmingly large amount of insulin. It is also easy to conceive of a slowly developing hypoglycemia with mild central nervous system symptoms which bring on an increase of physical activity, with a consequent rapid drop in the blood sugar. The rapid fall would then stimulate an increase in circulating epinephrine and the development of "adrenalin-like" symptoms.

From "Insulin Reactions" by Robert K. Maddock, M.D., and Leo P. Krall, M.D., in the A.M.A. *Archives of Internal Medicine*, June 1953.

Autonomic Neuropathy Simulating the Effects of Sympathectomy as a Complication of Diabetes Mellitus

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An association between diabetes mellitus and disorders of the nervous system was indicated as early as 1798 by John Rollo,[1] who, in his book, *Cases of Diabetes Mellitus,* noted the presence in diabetic patients of pain and paresthesia in the legs, as well as "lumbago and sciatica in so great degree as to deprive the use of the lower limbs." Frequency of neurologic abnormalities led many writers prior to 1850 to attribute diabetes to a lesion in the central nervous system. De Calvi,[2] however, in 1864, first recognized that diabetes might be the cause rather than the result of the nervous disturbance, and since that time, the literature on the subject of diabetic neuropathy has accumulated rapidly. Involvement of autonomic fibers of peripheral nerves was described by Auché[3] in 1890 and Pryce[4] in 1893, whereas abnormalities in the regulation of blood pressure, sweating and temperatures of the skin were first reported as late as 1945 by Rundles[5] and later by others.[6-13] Most reviews on the subject have been extensive and concerned primarily with the peripheral neuritis or "pseudotabes" of diabetes, but at present there appears still to be no unanimity of opinion regarding the pathogenesis of diabetic neuropathy. Rather than add still another review to the literature, our intent in this brief exposition is to describe our studies on three heretofore mentioned but not fully elucidated manifestations of diabetic neuropathy involving the autonomic nervous system, namely disturbance in sweating, temperature regulation and vasomotor control with resultant orthostatism.

METHOD OF STUDY

Certain patients suffering from diabetes mellitus and having one or more of the manifestations of disturbance in the autonomic nervous system which have been listed were selected for study. These patients were encountered in a period of 10 years and underwent one or more of the following studies in the course of examination at the Mayo Clinic:

1. *Physiologic Test of Thermoregulatory Sweating.*[14]

The cobalt chloride method was used to determine the regions of dyshidrosis. Cobalt chloride in a saturated solution in 95 per cent ethyl alcohol is deep blue in color but turns to bright pink on the addition of water. This solution was painted in stripes on the part of the body to be tested for anhidrosis. An aluminum heating cabinet, containing a series of incandescent light bulbs to maintain a temperature of about 140°F. and large enough to cover the entire body except for the head, was placed over the patient. After 10 minutes of heating in this cabinet, or whenever sweating occurred, the dots or stripes became a bright pink. The change in color of the stripes indicated the varying degrees of sweating with considerable accuracy. No change in color indicated anhidrosis.

2. *Skin Temperature.*

Basal metabolic rates were determined during a control period when basal measurements of the skin temperature of the fingers and toes were being carried out.

Before the tests the subjects fasted for 15 hours, and during the test they wore lightweight short pajamas and lay supine on comfortable beds. Data were obtained in a room in which the constant temperature was 25.5°C. (78°F.), and the relative humidity was 40 per cent. The temperature of the plantar surface of the first and third toes of both feet and the volar side of the distal phalanges of the first and third fingers was determined by means of copper-constantan thermocouples. The observations were made at intervals of 10 minutes for a period of 1 to 2 hours.

Read at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

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3. *Postural Blood Pressure.*

The blood pressure was determined with the subject lying on a tilt table and was recorded at varying degrees of tilting from 0 to 90°.

Additional studies were made as indicated on the patients selected. Methods to control the orthostatic hypotension were tried.

RESULTS OF STUDY IN GENERAL

In the 10-year period from Dec. 10, 1943, to Dec. 7, 1953, we carried out tests on 40 patients, each of whom exhibited one or more of the manifestations of diabetic neuropathy under consideration. This group consisted of 25 males and 15 females, the males outnumbering the females in a ratio of 1.7. Sixty-four per cent of the males and 60 per cent of the females were 40 years old or older, 36 per cent of the males and 33 per cent of the females were between 20 and 40 years of age (table 1). Duration of the disease prior to development of symptoms and signs under consideration ranged from 1 to 30 years; in 4 patients, the presence of diabetes had been known for less than 1 year. In 80 per cent of the males and 60 per cent of the females, the known duration of the disease had been 5 or more years (table 2). The diabetes was graded according to severity as follows: grade 1, very mild diabetes controllable by omission of concentrated sweets from the diet; grade 2, mild to moderate diabetes controllable by a diet containing up to 150 gm. of carbohydrate daily and requiring no insulin for control; grade 3, more severe diabetes, requiring diet, and up to 30 units of insulin daily; grade 4, severe diabetes requiring diet and more than 30 units of insulin daily. Ninety-six per cent of the males and 80.0 per cent of the females in the series had diabetes of either grade 3 or grade 4 (table 3). Associated findings indicating advanced involvement in other systems were recorded and are tabulated in table 4.

TABLE 1
Age and sex of patients

	Males		Females	
Age, years	No.	Per cent	No.	Per cent
10-19			1	6.7
20-29	4	16.0	3	20.0
30-39	5	20.0	2	13.3
40-49	6	24.0	1	6.7
50-59	5	20.0	5	33.3
60-69	4	16.0	1	6.7
70-79	1	4.0	2	13.3
Total	25	100.0	15	100.0

TABLE 2
Duration of diabetes

	Males		Females	
Duration, years	No.	Per cent	No.	Per cent
Less than 1	3	12.0	1	6.7
1-5	2	8.0	5	33.3
6-10	7	28.0	4	26.6
11-15	5	20.0	1	6.7
16-20	6	24.0	3	20.0
21-25	1	4.0	1	6.7
26-30	1	4.0	0	0
Total	25	100.0	15	100.0

TABLE 3
Severity of diabetes

Severity,	Males		Females	
grade	No.	Per cent	No.	Per cent
1			1	6.7
2	1	4	2	13.3
3	4	16	4	26.7
4	20	80	8	53.3
Total	25	100	15	100.0

TABLE 4
Autonomic neuropathy as a complication of diabetes

		Present	
Finding	Cases*	No.	Per cent
Vascular insufficiency	40	13	32.5
Retinopathy	38	27	71.1
Nephropathy	40	15	37.5
Peripheral neuropathy	40	35	87.5
Intestinal disorder	34	14	41.2
Bladder disorder	34	9	26.5
Impotence	6	6	100.0
Dyshidrosis	29	23	79.3
Vertigo and syncope	22	13	59.1
Orthostatic hypotension	20	16	80.0
Orthostatic tachycardia	19	4	21.1
Skin temperature	30	13†	43.3

*Cases in which finding was mentioned.
†Reversal of gradient from fingers to toes.

DYSHIDROSIS

Among its multiple functions, the autonomic nervous system supplies sudomotor fibers to the sweat glands. In the normal person, sweating is fairly even and diffuse over all portions of the body and occurs as one of the means of dissipating heat from the body when it is exposed to a warm environment. Any interference with the efferent pathways to the sweat glands results in an absence of sweating (anhidrosis) and a disturbance in the sweating pattern. It is well-known that in patients who have undergone bilateral lumbar or thoracolumbar sympathetic ganglionectomy for the treatment of essential

hypertension or other diseases, their ability to perspire below the level of sympathetic interruption is impaired (figure 1). In our series, 29 of the 40 patients had abnormal sweating patterns as determined by the method described (table 4). In 23 of the 29 (79.3 per cent) abnormal sweating indicated sudomotor involvement in varying degrees. In some cases, the regions of complete or partial anhidrosis were patchy in distribution; this observation suggested the possibility of peripheral sudomotor involvement (figure 2). In other cases, however, the line of demarcation was definite and almost identical to the pattern seen after sympathectomy; such an observation suggested involvement in the sympathetic trunks themselves.

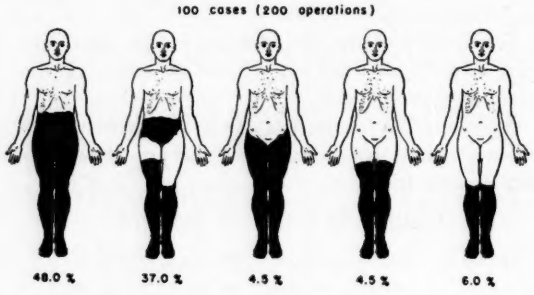

FIG. 1. Sweating tests following sympathectomy.

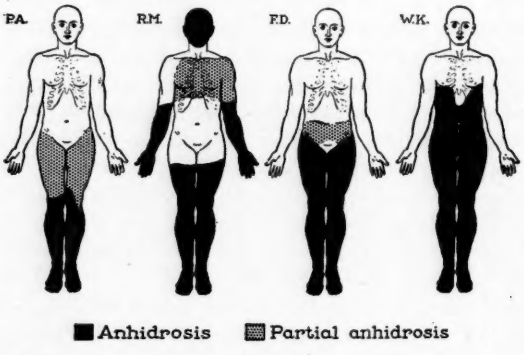

FIG. 2. Sweating pattern in autonomic neuropathy.

SKIN TEMPERATURE

In the normal individual the temperature of the body ordinarily is maintained at an essentially constant level of 98.6°F. (37.0°C.). To accomplish this, various physiologic mechanisms are continually operative, one of the major factors being the vasomotor regulatory mechanism. Under normal circumstances such as a room temperature of 25.5°C. (78°F.) there is a definite decreasing gradient in the skin temperature from the forehead to the fingers to the toes, the skin temperature of the toes being as much as 4° to 5°C. lower than that of the forehead. It has been shown that the level of the skin temperature of the toes will depend on the initial basal heat or the basal metabolic rate.[15-17] This gradient is present constantly, though less when the basal metabolic rate is particularly high. When vasomotor control to the lower extremities is interfered with, vasoconstriction no longer can occur as a means of preserving body heat, and the temperature of the lower extremities rises. Under such circumstances, the temperature gradient is distorted, and a so-called temperature reversal takes place (figure 3), that is, the skin temperature of the toes often is found to be higher than that of the fingers, particularly at normal room temperature.

This phenomenon, first reported by Sheard, Roth, Love and Horton[18] and more extensively by Roth and Craig,[19] has been found to occur routinely in patients who have had extensive bilateral sympathectomy. In fact such reversal is regarded as one of the criteria for a successful sympathectomy. Skin temperature studies were made on 30 of the patients in our series and 13 patients (43.3 per cent) showed reversal in the skin temperature gradient similar to that after extensive bilateral sympathectomy (figure 4).

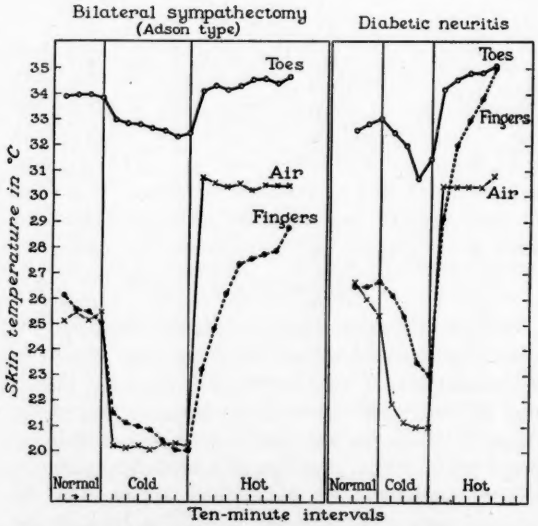

FIG. 3. Studies of skin temperature: comparison of sympathectomized patient with patient with diabetic neuropathy. Note reversal of temperature gradient between fingers and toes.

ORTHOSTATIC HYPOTENSION

Extensive studies of blood pressure were carried out in 20 of the 40 cases, and of this group, 16 patients (80.0 per cent) were found to have orthostatic hypotension of some degree (table 4). The symptoms and clinical manifestations of this phenomenon appeared to conform closely with the description of Bradbury and Eggleston,[20] who stated that the reactions are "what might be expected if the peripheral vascular bed were always wide open, inelastic and capable of accommodating the major proportion of the entire volume of the body." Whereas, under most circumstances of significant fall in blood pressure there is some degree of compensatory tachycardia, patients with true postural or orthostatic hypotension do not exhibit such tachycardia, and this has been considered to be one of the major factors in the production of vertigo and syncope (probably as a result of a decrease in cerebral blood flow (figure 5). Only 4 of the 19 patients studied (21.1 per cent) manifested compensatory tachycardia and none of these patients complained of vertigo or syncope (figure 6). However, in 13 (59.1 per cent) of the patients with orthostatic hypotension, vertigo and syncope were annoying or disabling symptoms. One patient was unable to stand, and in fact, had mild syncope when sitting erect.

Many measures were tried in an endeavor to correct the postural decrease in blood pressure. Epinephrine, norepinephrine, histamine (figure 6) levarterenol (levophed), aramine* (figures 7 and 8), paradrine† (figure 9) all have been found capable of elevating the blood pressure and holding it at asymptomatic levels as long as the administration of the drug was continued. However, stimulation by these drugs does not restore to the vasomotor system the ability to maintain the blood pressure level against the influence of gravity (figures 8 and 9).

Up to the present, in our experience, the only successful method for protecting such patients from the symptoms and physiologic effects of orthostatic hypotension has been wrapping the lower extremities from foot to thigh with elastic bandages and the application of a tight abdominal binder. Such measures have been employed and have been found successful in the treatment of orthostatic hypotension following sympathectomy. One might speculate on the possibility of such patients wearing a half G suit (such as those worn by combat aviators) for control of this disability.

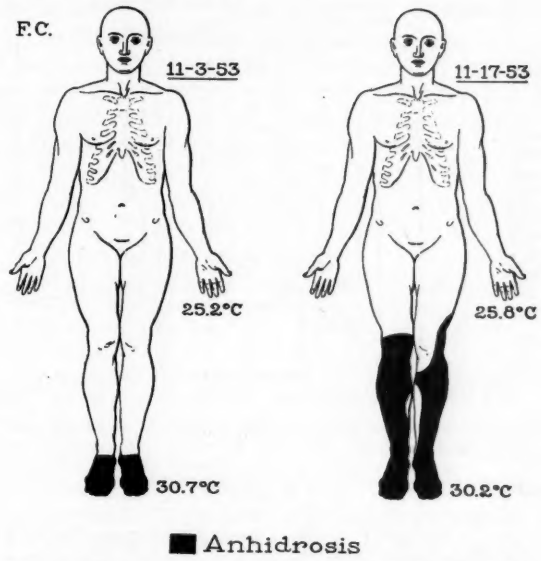

FIG. 4. Sweating patterns and skin temperatures in patient with diabetic neuropathy before and after bilateral lumbar sympathectomy (Adson type).

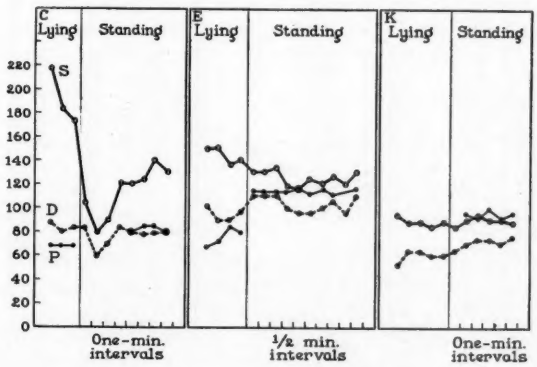

FIG. 5. Response of blood pressure to position.

COMMENT

This syndrome demonstrates the interesting use of laboratory methods in the everyday study of patients. As early as 1935 we observed, after extensive bilateral sympathetic ganglionectomy, lack of sweating or anhidrosis below the level of the surgical procedure. This was accompanied by a fall in blood pressure when the patient changed from the supine to the upright position. Likewise a reversal in the gradient of the skin temperatures occurred after extensive ganglionectomy, that is, the skin

*l-m-hydroxy-phenylisopropanolamine.

†α-phenyl-methylaminopropane hydrochloride.

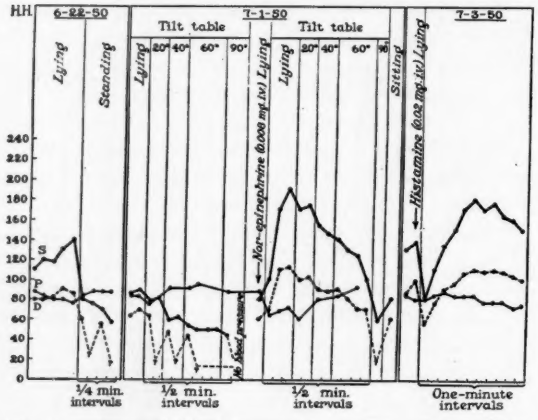

FIG. 6. Response of blood pressure to position, norepinephrine and histamine.

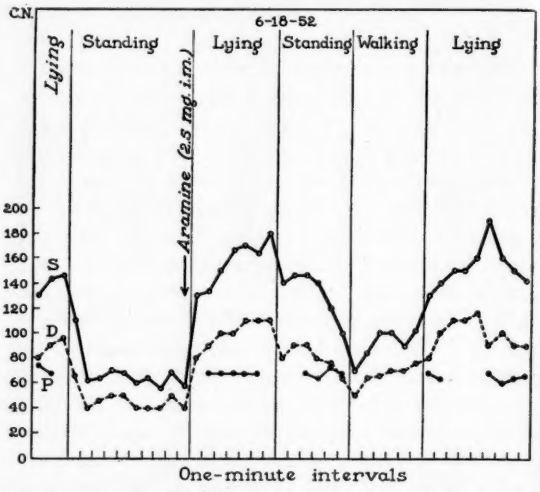

FIG. 7. Response of blood pressure to position and aramine on June 18, 1952.

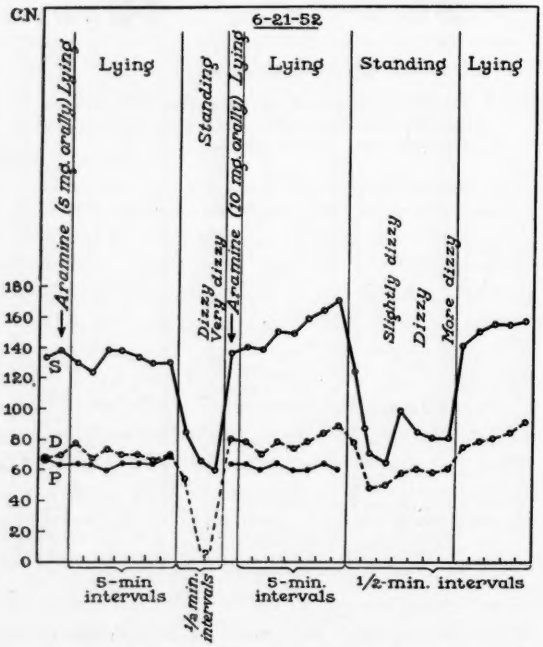

FIG. 8. Same patient as Fig. 7. Response of blood pressure to position and aramine on June 21, 1952.

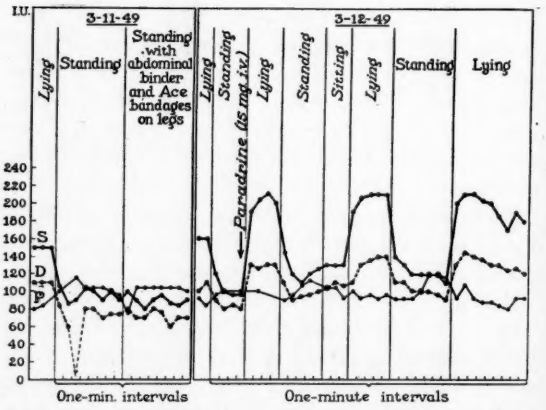

FIG. 9. Response of blood pressure to position and paradrine.

temperature of the toes was higher than that in the fingers and definite vasoconstriction was noted in the fingers as we have shown. At first this reversal of the skin temperatures was disturbing because the vasoconstriction in the fingers, that had been warm before operation, in some instances resembled that of Raynaud's disease. However, when the basal metabolic rates were determined, it was realized that the vasoconstriction in the hands was a physiologic response aimed at the conservation of heat, and that it occurred particularly in patients with low basal metabolic rates.

When the first patient with diabetic neuropathy in this group was sent to the laboratory for measurements of skin temperature to determine the extent of her peripheral vascular disease, we found that instead of vasoconstriction in her toes, the skin temperature of the toes was higher than that of the fingers. This was similar to the changes following extensive ganglionectomy but no sympathectomy had been performed. We then carried out sweating tests and postural blood pressures, the results of which indicated some disturbance of the sympathetic nervous system.

Whether this is a central or peripheral disturbance can only be partially solved. Two other studies in which we have used the same methods have demonstrated some speculative evidence. Head and Riddoch[21] have reported that after transection of the spinal cord when the spinal centers below the lesion are still intact, excessive sweating frequently occurs below the spinal lesion as a result of the mass reflex, because the spinal centers have been released from higher control and have established independent activity. In contrast, following removal of the entire spinal cord except the cervical and first thoracic segments by MacCarty[22] in an endeavor to remove a malignant astrocytoma, the anhidrosis was complete from the first thoracic segment down because all the spinal centers were removed. Thus if the lesion of the patients with diabetic neuropathy were in the spinal cord, excessive sweating rather than anhidrosis might have been present below the lesion.

DISCUSSION

Further studies[23] were carried out after Craig had performed two bilateral anterolateral chordotomies between the first and second thoracic vertebrae. These studies demonstrated disturbance of vasomotor function. In contrast to the pattern following bilateral extensive sympathectomy these 2 patients had a reversal of the skin temperature gradient of the toes even though thermoregulatory sweating was present. This observation indicates a dissociation between the sudomotor and vasomotor fibers in the spinal cord at that level. Apparently the vasomotor pathways were affected while sudomotor function remained intact. Since both the vasomotor and sudomotor activity were inhibited in the patients with diabetic neuropathy, the lesion would seem to be in the sympathetic nervous system distal to the cord.

SUMMARY

Orthostatic hypotension, frequently accompanied by vertigo and syncope, anhidrosis, and reversal in the skin temperature gradient from the fingers to the toes are expected sequelae of extensive lumbar or thoracolumbar sympathectomy.

One or all manifestations of this triad occur in a high percentage of patients with diabetes, and are thought to be related to diabetic neuropathy involving the autonomic nervous system. Studies made in 40 cases of diabetic neuropathy reported herein provided evidence for this hypothesis.

This disability appears to develop primarily in association with severe diabetes of long standing in older patients, and in association with other complications, such as arterial insufficiency, retinopathy, nephropathy and peripheral or visceral neuropathy.

Pharmacologic efforts to cure these patients or control the orthostatic hypotension have been unavailing, the only practical method in our experience being use of leg bandages and an abdominal binder.

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DISCUSSION

S. GORDON ROSS, M.D., (*Pasadena*): May I be the first to compliment Dr. Odel on his beautifully presented paper on autonomic neuropathies occurring in the diabetic.

Historically, a relationship between the autonomic nervous system and diabetes was first established by Claude Bernard in his classical paper in *Piqûre Diabetique*, published in 1849.

In this paper, the symptoms presented represent dysfunctions, namely: abnormal patterns of sweating, abnormal temperature changes in the extremities, abnormal blood pressure adjustments to posture. In the overall function of the autonomic nervous system in maintaining homeostasis, we find that these symptoms have to do with the conservation of body energy. Now, diabetes is also a major fault in body homeostasis that has to do with energy. In this relationship to energy, once more we find that the autonomic nervous system and diabetes have a common denominator.

The autonomic neuropathies recorded by Dr. Odel deserve more attention. We are seeing more changes associated with vascular degeneration and more cases of intractable diarrhea. I should like to ask Dr. Odel if in his clinical experience there is an increasing incidence of these symptoms he describes as the years pass by.

THOMAS MCGAVACK, M.D., (*New York*): Did Dr. Odel find that the incidence of these autonomic nervous system conditions or manifestations varied in relation to the incidence and severity of peripheral neuritis or in relation to the amount of atherosclerosis demonstrable in the body generally?

Dr. Odel has described the incidence of this autonomic nervous system syndrome in patients with diabetes mellitus. Has he observed its incidence in totally unrelated disease? In other words, is the relationship of the syndrome to diabetes mellitus one of cause-and-effect, or one of pure chance?

HOWARD M. ODEL, M.D., (*Rochester, Minnesota*): In answer to Dr. Ross, I am not sure we are seeing this condition more frequently. We recognized our first case in 1946. At that time we went back to 1943 and picked up about five or six patients who had had studies and had not been thoroughly documented. I think any increase in incidence is more apparent than real. We are more conscious of the syndrome, and when we see a diabetic patient with neuropathy, we immediately arrange to have him studied in Dr. Roth's laboratory.

Dr. McGavack, I have no information regarding the incidence of this symptom complex in unrelated conditions. It would be interesting to study a group of diabetics without other complications to see how many will have abnormalities in sweating patterns, and any latent tendency toward orthostatic hypotension. I doubt that many will have true postural hypotension. That is usually a presenting symptom. Also, there were only five of our cases in which there was no evidence of peripheral neuropathy.

SUMMARIO IN INTERLINGUA

Neuropathia Autonome Simulante le Effectos de Sympathectomia Como Complication de Diabete Mellite

Hypotension orthostatic (frequentemente accompaniate de vertigine e syncope), anhidrosis, e le si-appellate reversion del gradiente de temperatura cutanee inter le digitos del mano e le digitos del pede es expectate sequelas de extense sympathectomia lumbar o thoracolumbar.

Le manifestationes de iste triade occurre insimul o individualmente in un alte procentage de patientes con diabete e pare relationate a neuropathia diabetic afficiente le autonome systema nervose. Iste hypothese es supportate per le hic-reportate studio de 40 casos de neuropathia diabetic.

Il para que iste invaliditate se disveloppa primarimente in association con sever diabete de longe durantia in patientes de etate avantiate e in plus in association con altere complicationes (como insufficientia arterial, retinopathia, nephropathia, e neuropathia peripheric o visceral).

Effortios pharmacologic a curar iste patientes o a continer lor hypotension orthostatic se ha provate van. Secundo nostre experientia le sol methodo practic es le uso de bandages gambier e de bandas abdominal.

The Diagnosis and Treatment of Pyelonephritis in Diabetes Mellitus

Guy E. Joron, M.D., Joan deVries, M.D.,† Grant Reid, M.D.,‡ William H. Mathews, M.D.,§ and Joseph W. McKay, M.D.,|| Montreal*

The purpose of the study reported here was to establish criteria for the clinical diagnosis of pyelonephritis in diabetic patients and to assess the recommended methods of treatment.

Pyelonephritis in diabetes has received much attention from pathologists in recent years. Autopsies have revealed pyelonephritis in 18 to 22 per cent of diabetics, in contrast to 3 to 4 per cent of the general population.[1-5] In addition, a peculiar complication of acute pyelonephritis called renal medullary necrosis, necrosis of the renal papillae or necrotizing papillitis is found much more commonly in diabetics than in nondiabetics.[5-10]

The diagnosis of pyelonephritis is not made nearly so frequently by clinicians. Diabetic patients may not present the usually described picture of acute pyelonephritis with chills and loin pain. Frequency and burning on urination may be absent or, if present, attributed to the diabetes. In the great majority of cases there are no subjective symptoms or physical signs to direct attention to an infective process involving the kidneys.

The treatment of pyelonephritis still leaves much to be desired, but the development of new antibacterial agents has permitted the development of increasingly effective methods of treatment.[11-12]

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||Director, Dept. of Radiology, Montreal General Hospital; Associate Professor of Radiology, McGill University.

CULTURES OF BLADDER URINE

Our point of departure was to obtain cultures of bladder urine in diabetic patients and equivalent nondiabetic controls. The patients were those attending the outdoor clinics or admitted to the wards of the Montreal General Hospital. Patients admitted directly to the Urological Service were not included. Catheter specimens of urine were obtained in females and mid-stream voided specimens in males.

In table 1 are summarized the results of bladder urine cultures in 409 diabetic patients and 280 controls. The age distributions of the two groups were identical and, except for the absence of children, corresponded roughly to the usual age distribution of a diabetic population. The average age of the males was 56 years and of the females 60 years. Positive urine cultures were found in 61 per cent of diabetic men and women, compared with 59 per cent of male controls and 43 per cent of female controls. The high incidence of infection in men of both groups was unexpected. It is perhaps accounted for by the high average age of the series. These are the results found on first culture. Ideally in each case one should have two or three urine cultures which check. The magnitude of the task of securing repeated cultures in a series of ambulatory patients sufficiently large to be significant and the danger of repeated catheterization in women made this impractical. Pyuria was found more than twice as often in diabetics as in nondiabetics—in 19 per cent of diabetic men and 25 per cent of diabetic women compared with 9 per cent of both male and female controls.

Table 1 also shows the types of organisms encountered. *Escherichia coli* was the predominating organism in women but was rare in men. All other organisms were found more frequently in men than in women.

CULTURES OF URETERAL URINE AND RETROGRADE PYELOGRAMS

The next step was to select a group of 41 diabetics who had positive bladder urine cultures but no urinary complaints. On direct questioning, a small proportion

TABLE 1

Incidence of positive cultures of bladder urine in diabetics and controls

Types of cases studied	No. of cases	Per cent positive	Types of organisms (no. of cases)					
			Esch. Coli	Staph. Pyogenes	Aerob. Aerogenes	Strepto-cocci	Others	Mixtures
150 male diabetics	92	61						
with pyuria	29	19	2	5	5	3	8	6
without pyuria	63	42	3	11	5	15	8	21
259 female diabetics	158	61						
with pyuria	66	25	34	4	9	2	5	12
without pyuria	92	36	25	9	6	25	6	21
150 male controls	88	59						
with pyuria	13	9	6	1	3	2	0	1
without pyuria	75	50	11	12	9	9	17	17
130 female controls	56	43						
with pyuria	12	9	6	2	0	2	1	1
without pyuria	44	34	16	1	5	7	5	10

admitted occasional burning on urination and bouts of frequency, but none had come to the hospital seeking relief from these symptoms. Ureteral cultures and retrograde pyelograms were obtained in these cases. Table 2 shows the results of the ureteral cultures. Group 1 consists of cases in which the bladder cultures yielded the same organism on two or more occasions and pus was noted on the smear. In each of these patients the same organism was recovered from one or both ureters. Group 2 consists of cases in which the bladder cultures showed growth of the same organism, but no pus was found. The same organism was also recovered from the ureters in half the cases. In group 3, the same organism was not found on repeated bladder cultures and no organisms were recovered from the ureters. We conclude that the 25 patients with positive ureteral cultures had pyelonephritis, notwithstanding the paucity of symptoms. The 8 members of group 2 with positive ureteral cultures will probably belong to group 1 in due course. We are following several diabetics who repeatedly have the same organism in the urine but show no pyuria. Two such men at first had no pyuria, but then developed it, and eventually at autopsy the organism which had been found in the urine was recovered from the pelvis of the kidney. Grossly there was mild pyelitis and microscopically a necrotizing papillitis. In neither case was the diabetes or the renal lesion the cause of death.

TABLE 2

Cultures of ureteral urine in 41 diabetics with positive cultures of bladder urine

Bladder urine cultures	No. of cases	Ureteral urine cultures	
		Positive	Negative
1. Growth of same organism on repeated culture, plus pyuria.	17	17	0
2. Growth of same organism on repeated culture, no pyuria.	17	8	9
3. Growth of different organism, on repeated culture.	7	0	7

The evidence presented suggests that pyelonephritis is present or likely to develop if the same organism is recovered repeatedly from the bladder urine, particularly if there is associated pyuria.

The retrograde pyelograms done in this group of 41 cases were of little help so far as the diagnosis of pyelonephritis was concerned. This is in conformity with our previous experience with pyelography, retrograde or intravenous, in pyelonephritis. The calyceal pattern is perhaps not so delicate or one may note blunting of the papillae, but on the whole there is poor correlation with

bacteriologic and autopsy findings. The main value of pyelography lies in the exclusion of other lesions.

EVIDENCES OF RENAL DAMAGE AND SYSTEMIC TOXICITY

Although the urinary findings are often the only indication of renal infection, there may be evidences of renal damage and systemic toxicity. The most important of these evidences are nitrogen retention, anemia, fever, fatigue, loss of appetite and loss of weight. When present, these may suggest the diagnosis and lead to a search for bacteria and pus in the urine.

Acute pyelonephritis deserves special mention. In our experience, acute pyelonephritis in diabetics almost always masquerades as something else. It is rarely diagnosed unless one keeps it constantly in mind and examines the urine repeatedly. The most striking feature has been prostration out of all proportion to the physical signs. There may be vague abdominal pain and tenderness—hardly ever in the costovertebral angle—fever and chills, nausea, vomiting, and drowsiness.

There are three common errors in diagnosis. The first is to blame the situation solely on uncontrolled diabetes —not unjustifiably in view of the clinical picture and the presence of hyperglycemia due to diabetes, acetonuria due to vomiting, and acidosis due to renal failure. The second error is to assume the presence of a lesion of the gastrointestinal tract such as diverticulitis, cholecystitis, or intestinal obstruction. The third error is to rule out pyelonephritis because the voided urine does not contain pus cells. Patients who are confined to bed and have residual urine in the bladder may void only relatively clear supernatant urine free from pus, whereas the last portion of a catheter specimen may show gross pyuria. Repeated cultures and microscopic examinations of catheter specimens of urine are required to establish the diagnosis.

TREATMENT

Treatment is none too satisfactory. There is a tendency to relapse and the infecting organisms may become resistant to the antibacterial agent in use. This latter event can be serious. We have seen cases of apparently mild asymptomatic pyelonephritis react to treatment by a change in bacterial flora with sudden development of acute symptoms and septicemia. In other cases, after a prolonged trial with appropriate antibacterial agents, changing the drug with changes in culture, we have ended with an organism apparently resistant to all agents. Accordingly, the intensity with which we pursue therapy depends on our clinical assessment of the gravity of the case. For this purpose, we recognize three types of pyelonephritis: (1) chronic pyelonephritis with evidence of renal damage or systemic toxicity; (2) chronic pyelonephritis without evidence of renal damage or systemic toxicity; and (3) acute pyelonephritis.

Chronic Pyelonephritis with Evidence of Renal Damage or Systemic Toxicity

In these cases we have given prolonged treatment with appropriate antibacterial agents in the usually recommended dosages. Frequent urine cultures with sensitivity tests are required to ensure that a change in drug is not indicated. We believe that a wide-spectrum antibiotic is more likely to succeed and have used Terramycin orally as our first choice. A variety of antibacterial agents have been employed. Encouraging results have been obtained with Furadantin in Proteus infections and with Aerosporin in certain cases due to Pseudomonas. Organisms resistant to these drugs have usually responded to Chloromycetin. Sulfonamides such as Thiosulfil and Gantrisin have been employed following courses of antibiotic therapy. Treatment generally brings rapid improvement in the patient's sense of well-being, often before there is any change in the urinary findings.

Chronic Pyelonephritis without Evidence of Renal Damage or Systemic Toxicity

In these cases we recommend a two-week course of treatment with an appropriate antibacterial agent. At the end of this period some cases will be cured. If not, the course may be repeated in special circumstances, but we think it unwise to pursue therapy indefinitely in every case until the urine remains sterile. It must be remembered that many patients have chronic urinary tract infection for decades without much evidence of harm. Such a patient must of course be kept under observation to ensure that serious trouble does not develop.

Acute Pyelonephritis

The treatment of acute pyelonephritis must be intensive from the start, since the disease may rapidly become fatal. We prefer large doses of Chloromycetin parenterally. Prompt action of an effective wide-spectrum antibiotic is thus ensured. Later results of blood and urine cultures may necessitate a change in therapy.

SUMMARY

Pyelonephritis is a common postmortem finding in diabetics but is often unrecognized during life. The object of this study was to establish criteria for the clinical diagnosis of pyelonephritis and to assess the recommended methods of treatment.

Specimens of bladder urine were obtained from 409 diabetics and 280 equivalent nondiabetic controls. The

incidence of positive cultures was high in both the diabetic and nondiabetic groups—in 61 per cent of both male and female diabetic patients, in 59 per cent of male controls and in 43 per cent of female controls. The incidence of pyuria was substantially higher in the diabetic group—in 19 per cent of male, 25 per cent of female diabetics compared with 9 per cent of both male and female controls.

Forty-one patients with positive cultures of bladder urine but without urinary complaints were cystoscoped, and cultures of ureteral urine and retrograde pyelograms were obtained. The results suggest that pyelonephritis is present or likely to develop if the same organism is recovered repeatedly from the bladder urine, particularly if there is associated pyuria.

Pyelography was of little help in so far as the diagnosis of pyelonephritis was concerned.

Three types of pyelonephritis are recognized clinically: (1) chronic pyelonephritis without evidence of renal damage or systemic toxicity; (2) chronic pyelonephritis with evidence of renal damage or systemic toxicity; and (3) acute pyelonephritis. The clinical features and treatment of these three types are described.

Antibacterial therapy with careful bacteriologic control has much to offer in selected cases.

ACKNOWLEDGMENT

The assistance of the Banting Research Foundation is gratefully acknowledged.

We wish to thank the following companies who generously donated the antibacterial agents used in this study: Pfizer Canada, Ltd., for Terramycin; Parke, Davis & Co., Ltd., for Chloromycetin; Burroughs Wellcome & Co., Inc., for Aerosporin; Ayerst, McKenna & Harrison, Ltd., for Thiosulfil; Eaton Laboratories for Furadantin; Hoffmann-La Roche, Ltd., for Gantrisin.

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DISCUSSION

HOWARD F. ROOT, M.D., (*Boston*): The authors report an extensive experience and careful bacteriological study of urinary cultures in 409 diabetics and 280 controls. Their findings of positive urinary cultures plus pyuria in 25 per cent of diabetic women and in 19 per cent of diabetic men in contrast to 9 per cent of male and female controls is itself a striking evidence of the frequency of urinary tract infections in diabetic patients.

I should like to emphasize the predominance of the colon bacilli in the urine of women in contrast to the men because this was exactly the same type of finding which we made in a series of patients studied at the New England Deaconess Hospital. In our series, among the first 52 diabetic patients referred for special follow-up treatment of urinary tract infections, 51 were women. It seemed reasonable that the predominance of bacteria commonly found in the colon might indicate the possibility of urethral contamination since blood-born infections should occur with equal frequency in the two sexes. Improved teaching and practice in rectal and perineal hygiene might prevent many such infections. In a series of women who came to us not one of them admitted ever having been instructed to cleanse away from the vagina after bowel movements in an effort to prevent urethral contamination, although pediatricians commonly so advise mothers in the care of female children. Because of the well-known frequency of diarrhea in diabetes it might well become part of the teaching, first for young women discovered to have diabetes, and especially those in whom some degree of pruritus has resulted in traumatic perineal and vulvar lesions.

It is also important to point to their comments upon the seriousness of pyelonephritis even in the absence of

the common symptoms of fever, abdominal pain, nausea and vomiting. The most severe involvement of the kidneys may be present without any of the ordinary classical symptoms.

The difficulties of checking bacilluria were great in our cases. We accepted as cured only those patients who after a period of treatment, very often months in duration, had three separate and final bacteriological cultures entirely negative and in whom also there were no symptoms or evidences of kidney damage. One would like to emphasize again conclusions which the authors have arrived at with respect to the frequency and the seriousness of the urinary-tract infection and the ease with which the diagnosis may be overlooked and also the value of the new antibiotics. In our cases, as in theirs, sensitivity tests for the organisms obtained often gave important clues as to which drug should be used. On the other hand, these sensitivity tests were not always consistent with the results of treatment. In some cases, a combination of drugs such as Chloromycetin, Streptomycin and Aureomycin were effective.

The relation of pyelonephritis and the progressive development of the diabetic nephropathy (or Kimmelsteil-Wilson syndrome) needs further study. In all of our diabetics with onset in childhood, who died after having diabetes at least 12 years, the characteristic lesions in the glomeruli, described by Kimmelsteil and Wilson were present, but always associated were the pathologic evidences of pyelonephritis of varying degrees of severity.

SUMMARIO IN INTERLINGUA

Le Diagnose e Tractamento de Pyelonephritis in Diabete Mellite

Le constatation post morte de pyelonephritis es frequente in casos de diabete, sed durante le vita del patiente iste condition es frequentemente inrecognoscite. Le objectivo del presente studio es establir criterios pro le diagnose clinic de pyelonephritis e evalutar le recommendate methodos therapeutic.

Esseva obtenite specimens de urina ab le vesicas de 409 diabeticos e 280 equivalente nondiabeticos de controlo. Le frequentia de culturas positive esseva alte in ambe gruppos: 61 pro cento pro diabeticos mascule, le mesmo pro diabeticos feminin, 59 pro cento pro le masculos de controlo, e 43 pro cento pro le femininas de controlo. Le frequentia de pyuria esseva plus alte in diabeticos que in nondiabeticos: 19 pro cento pro diabeticos mascule, 25 pro cento pro diabeticos feminin, 9 pro cento pro masculos de controlo, e le mesmo pro femininas de controlo.

Examines cystoscopic esseva executate in 41 patientes con positive culturas del urina vesical sed sin difficultates urinari. In iste casos culturas de urina ureteral esseva obtenite e etiam pyelogrammas retrograde. Le resultatos supporta le conclusion que pyelonephritis es presente o imminente in casos in que le mesme organismo es obtenite repetitemente ab le urina vesical. Isto es specialmente ver in casos characterisate per le presentia de pyuria.

Pyelographia non esseva de grande adjuta in le diagnose de pyelonephritis.

Tres typos de pyelonephritis es clinicamente recognoscite: (1) Chronic pyelonephritis sin evidentia de lesion renal o de toxicitate systemic; (2) chronic pyelonephritis con evidentia de lesion renal o toxicitate systemic; e (3) pyelonephritis acute. Le characteristicas clinic e le therapia de iste tres typos es describite.

Therapia antibacterial—usate sub exigente conditiones de controlo bacteriologic—ha multo a offerer in seligite casos.

Nutritive Value of Milk

New evidence that pasteurized milk is just as nutritious as raw milk and that milk's food value does not change with the seasons is reported in a recent issue of the American Chemical Society's *Journal of Agricultural and Food Chemistry* by Conrad A. Elvehjem, chairman of the University of Wisconsin's department of biochemistry, and John N. Bixby, Arthur J. Bosch, and Arthur M. Swanson of the departments of biochemistry and dairy and food industries. Contradicting the results of some earlier experiments, the group's extensive tests with white rats show that neither pasteurizing nor homogenizing milk has an adverse effect on its nutritive qualities and that fresh milk is no less nourishing in winter than in summer.

From *Science*, Oct. 15, 1954

Effect of Intravenously Administered Fructose on Blood Acid-Base Balance in Patients with Pre-existing Acidosis

Oscar R. Kruesi, M.D., Maurice F. Goodbody, Jr., M.D., Theodore B. Van Itallie, M.D., and James G. Hilton, M.D., New York

Recently there has been a greatly increased use of fructose as a source of carbohydrate and calories in parenteral alimentation. Since it has been shown that metabolism of fructose in patients with diabetes mellitus proceeds readily even in the absence of insulin,[1,2] intravenous fructose is being employed as an adjunct in the treatment of diabetic acidosis and insulin-resistant diabetes.

The observation has been made that administration of fructose produces a greater increase in blood pyruvic and lactic acid levels than does administration of a comparable amount of glucose.[1-4] This effect has been noted in both normal and diabetic subjects. The question arises whether this increase in organic acids may become of sufficient magnitude to have an adverse effect in patients with pre-existing respiratory or metabolic acidosis.

Weichselbaum, Margraf and Elman[5] have reported minimal alterations in blood *p*H and plasma bicarbonate levels in normal individuals given a liter of 10 per cent fructose at a rapid rate; however, in two patients under anesthesia given similar quantities of fructose, an appreciable decrease in *p*H and bicarbonate values apparently ensued. Since acid-base changes known to occur as a result of anesthesia alone[6,7] were not controlled in Weichselbaum's experiments, we considered it important to reexamine these fructose-induced effects, not only in patients under anesthesia, but also in patients with pre-existing acid-base derangements associated with a variety of clinical states.

SUBJECTS AND PROCEDURE

Studies were performed on 20 patients. Of these, 8 were in normal acid-base balance, 9 were in metabolic acidosis in various stages of compensation, 2 were in respiratory acidosis induced by pentothal anesthesia, and 1 was in metabolic alkalosis due to vomiting. The metabolic acidosis group consisted of 6 normal subjects given ammonium chloride orally in a dose of 1.5 mEq./kg. of body weight per day for 3 to 10 days prior to the fructose infusion. There were also 3 patients studied who had chronic glomerulonephritis with reduced renal reserve. All subjects studied, with the exception of the 3 with glomerulonephritis, were free of respiratory, renal, or hepatic dysfunction.

The subjects ordinarily were given 1000 ml. (range 500 to 1600 ml.) of 10 per cent fructose in water (Levugen[R]) intravenously at rates varying between 0.36 and 1.23 gm. per kg. of body weight per hour. Blood samples were taken immediately before and after infusion (table 1). In some instances, samples also were taken frequently during infusion.

METHODS OF ANALYSIS

In the 2 anesthetized patients analyses were performed on specimens obtained by direct brachial artery puncture. All other analyses were performed on arterialized venous blood, which were drawn under oil from an antecubital vein by the method of Davenport.[8] All blood samples were promptly analyzed for *p*H level and carbon dioxide content. The *p*H was determined on whole blood at room temperature by means of a Beckman model G *p*H meter. Appropriate correction to body temperature was made by subtracting 0.014 *p*H units per centigrade degree difference between room and body temperatures. The carbon dioxide content of plasma was measured by the manometric method of Van Slyke and Neill.[9] Bicarbonate concentration was calculated according to the Henderson-Hasselbach equation. A *p*K of 6.1 was used for carbonic acid in this calculation.

RESULTS AND DISCUSSION

The blood *p*H and plasma bicarbonate values for each subject before and after fructose infusion are given in

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table 1. In almost every instance these values decreased slightly following fructose administration. At no time was any marked fall in *p*H or bicarbonate observed.

TABLE 1

Blood *p*H and plasma bicarbonate levels immediately prior to and at end of fructose infusion

Patient	*p*H*	HCO_3,* mEq./L.	Fructose ml. 10% sol.	Infusion rate gm./kg./hr.	*p*H†	HCO_3† mEq./L.
			Normal			
P.A.	7.42	25.7	1,000	0.94	7.35	23.1
C.R.	7.40	22.1	1,000	1.01	7.35	19.4
D.I.	7.38	24.2	1,000	1.04	7.33	22.1
W.I.	7.36	26.1	1,000	1.21	7.32	23.3
G.R.	7.37	26.5	1,000	1.20	7.33	22.0
N.A.	7.41	24.8	1,000	1.05	7.36	20.3
K.E.	7.43	24.2	1,000	1.23	7.37	19.5
W.L.	7.39	24.4	1,000	1.15	7.37	22.1
Average	7.39	24.7			7.34	21.4
			Metabolic Acidosis			
H.A.	7.31	19.1	500	0.96	7.41	18.4
G.O.	7.41	29.8	1,000	1.23	7.25	26.2
L.I.	7.36	27.5	1,000	1.21	7.26	22.5
H.R.	7.33	18.6	1,000	1.06	7.28	19.4
W.S.	7.34	22.9	1,000	1.11	7.31	19.5
N.L.	7.37	22.0	1,000	1.18	7.34	17.6
L.O.	7.41	22.5	1,300	0.76	7.38	23.8
R.O.	7.43	25.1	1,300	0.46	7.36	21.0
R.D.	7.36	23.8	1,600	0.36	7.44	24.8
Average	7.36	23.5			7.34	21.5
			Anesthesia			
M.O.	7.29	22.9	1,000	0.91	7.24	18.9
F.T.	7.23	27.7	900	0.85	7.30	23.0
			Metabolic Alkalosis			
A.L.	7.40	31.4	1,000	0.92	7.35	29.5

*Before fructose administration.
†At the end of fructose infusion.

In the normal subjects, the average fall in *p*H was 0.05 units. In the same group, the average fall in bicarbonate was 3.3 mEq./L. In the patients with metabolic acidosis, the average fall in *p*H was 0.02 units .The average decrease in bicarbonate concentration was 2 mEq./L.

The patients with uncompensated metabolic acidosis did not exhibit changes in *p*H and bicarbonate greater than those observed in the compensated group. Similar minor decreases in *p*H and bicarbonate after fructose administration were seen in the two patients under anesthesia and also in the single patient with metabolic alkalosis.

There was no evidence that the slight degree of acidosis which occurred as a result of fructose administration produced any of the manifestations ordinarily associated with clinical acidosis. Accordingly, we consider these slight changes to be of no clinical significance.

In figure 1 are shown serial blood *p*H and plasma bicarbonate values during the entire course of an infusion of fructose given rapidly to a patient under anesthesia. Control samples prior to fructose administration were taken after anesthesia had begun because of the known effect of induction of anesthesia alone on acid-base balance.[6, 7] It was hoped that in this way a distinction could be made between anesthesia-induced acidosis and any additional effect that fructose itself might have had on acid-base balance during the course of anesthesia.

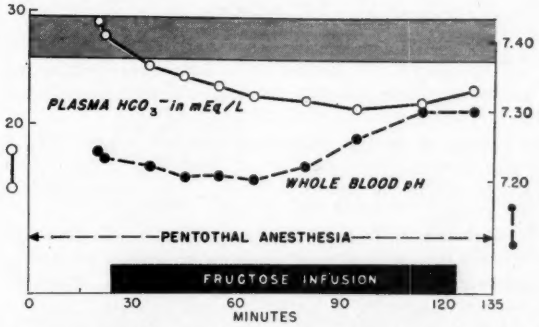

FIG. 1. Patient F. T. Effect of 900 cc. of 10 per cent fructose administered intravenously at the rate of 0.85 gm. per kg. per hr. on blood pH and plasma bicarbonate in an anesthetized patient. (Shaded area represents approximate normal range of pH and bicarbonate in unanesthetized persons. Slight rise in pH after 60 minutes was associated with improved ventilation; high values for bicarbonate early in anesthesia were associated with restricted ventilation.)

It is apparent that the control *p*H and bicarbonate values twenty minutes after induction of anesthesia were definitely low, indicating an acute respiratory acidosis due to anesthesia alone. Subsequent administration of 90 gm. of fructose did not appear to increase the severity of the acidosis.

Taken as a whole, the findings indicate that infusions providing 50 to 160 gm. of fructose at rates ranging from 0.36 to 1.23 gm. per kg. of body weight per hour induce small but consistent decreases in blood *p*H levels and plasma bicarbonate concentrations. It seems reasonable to attribute such changes to the increased production of organic acids which accompanies fructose catabolism.

These changes in acid-base balance do not appear to be of clinical significance, either in the normal individual or in patients with pre-existing acidosis.

SUMMARY

1. The effect of intravenously administered fructose on blood *p*H and plasma bicarbonate levels was determined in normal subjects, patients with ammonium chloride-induced acidosis, patients with metabolic acidosis associated with chronic renal insufficiency, and patients with respiratory acidosis induced by anesthesia.

2. Fifty to 160 gm. of fructose in water given at rates varying between 0.36 and 1.23 gm. per kg. of body weight per hour produced small but consistent decreases in blood *p*H and plasma bicarbonate levels in most of the subjects studied.

3. These minor chemical changes were unaccompanied by clinical manifestations of acidosis.

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SUMMARIO IN INTERLINGUA

Le Effecto de Fructosa, Administrate per Via Intravenose, Super le Balancia de Acido e Base in le Sanguine de Patientes con Pre-existente Acidosis

1. Le effecto de fructosa, administrate per via intravenose, super le nivellos de *p*H del sanguine e de bicarbonato del plasma esseva determinate in (a) subjectos normal, (b) patientes con acidosis inducite per chlorido de ammonium, (c) patientes con acidosis metabolic associate con chronic insufficientia renal, e (d) patientes con acidosis respiratori inducite per anesthesia.

2. Inter 50 e 160 g fructosa in aqua, administrate in ratas variante inter 0,36 e 1,23 g per kg peso corporee per hora, produceva in le majoritate del subjectos studiate un leve sed consequente reduction del nivellos de *p*H del sanguine e de bicarbonato del plasma.

3. Iste minor cambiamentos chimic non esseva accompaniate de manifestationes clinic de acidosis.

Management of Lesions of the Feet in Diabetes

Methods Recommended by the Diabetes Service at the Boston City Hospital

David Hurwitz, M.D., Boston*

Lesions affecting the feet in cases of diabetes are among the most frequent and perplexing complications of this disease. About two-thirds of the approximately sixty diabetic in-patients at the Boston City Hospital are admitted for infections or gangrene of the toes or feet. Diabetics rarely need admission for regulation or for acidosis, so that most of the patients seen by the Diabetes Service suffer from foot complications. In the last ten years there has been a change toward conservative management of these conditions, largely as a result of the use of antibiotics. Such management requires prolonged periods of hospitalization and thus places a heavy burden on municipal and community hospitals, which can carry the load only by having a well organized diabetes service.

With its increased experience, the Diabetes Service is in a position to offer valuable suggestions in the handling of these patients. In the past, the surgeon often felt compelled to do a high amputation to get beyond the infection. Now he knows it is unlikely that infection will spread once antibiotic therapy has begun. Fear of wide incision into and drainage of infected areas in the diabetic patient is without basis now that antibiotics are available, and local accumulations of pus should be widely drained early in a manner similar to the procedure for comparable lesions in the nondiabetic. Unfortunately, pus even when under pressure is too often tolerated by the surgeon because of his reluctance to cut into an infected area in a diabetic. This attitude is no longer tenable. It is often the duty of the internist to urge the surgeon to disregard the diabetes in dealing with foot infections.

After initial drainage, the foot should be inspected and dressed daily, since often further pockets requiring drainage will be found. Not infrequently three to five trips to the operating room may be necessary. Occasionally, one or more digits or metatarsals must be sacrificed because of osteomyelitis and because of the need for adequate drainage. After slough has been removed and the infection has quieted down, the foot shows remarkably rapid healing, often without necessitating plastic surgery. This might occur even in the absence of palpable dorsalis pedis pulse which often returns after subsidence of edema.

In general the plan of treatment of patients with foot infections which my colleagues and I employ is as follows:

1. All patients, including those with even minor foot infections, are hospitalized. They are given a complete physical examination to rule out other complications.

2. An adequate diet as high as possible in proteins is ordered. This is important since the nutritional state of these patients is often poor, and even if the diabetes is well controlled good healing does not take place unless caloric and total nutritional needs are filled.

3. Diabetes should be well controlled. These patients often require much more than their usual dosage of insulin when infection is present. We attempt to get the urine tests as close to sugar free as possible without provoking hypoglycemia.

4. Cultures and sensitivity studies are obtained from the infected areas and appropriate antibiotics given. If no open lesion is present, penicillin should be given in doses of 600,000 to 1,000,000 units daily.

5. Wide drainage of the infected area should be done within twenty-four hours of admission and repeated according to need thereafter.

If this plan is carried out, high amputations are rarely necessary. Since most of these patients are in the older age group and likely to have difficulty in learning to use a prosthesis, high amputations result in a chair-and-bed existence with consequent drain on family and community resources and demoralization of the patient. Weeks or months of hospitalization are worth-while if the patient can eventually walk out on his own two feet.

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Presented at a meeting of the New England Diabetes Association, Nov. 2, 1953.

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Our rule is that no high amputation should be done for infections of the feet unless two weeks of conservative treatment have elapsed, and by that time it is rarely necessary.

The results of conservative treatment of gangrene are often good, but they are by no means as encouraging as is the case with infections. A gangrenous toe may be removed without the need of further surgery. Often these patients require a transmetatarsal or high amputation. It is important to differentiate true early gangrene from necrotic slough due to infection, since the latter usually carries a better prognosis. If higher amputations are necessary, we have recently advised below-knee amputation, provided there is a good popliteal pulsation, and the patient can be considered to be a candidate for a prosthesis since below-knee prostheses are better functionally. The contribution of lumbar sympathectomy is doubtful and difficult to evaluate. Often it is performed because there is nothing else to be done. In three of the cases described below, sympathectomy was performed, but the improvement in the foot lesions was not dramatically affected. We do not recommend this procedure routinely in foot lesions associated with diabetic arteriosclerotic disease.

The following cases illustrate the principles discussed above.

Case 1. Mrs. McI., a sixty-year-old woman, was admitted to the Boston City Hospital because of an infection occurring after her foot had been stepped on two weeks previously. She had symptoms of polydipsia, polyuria, and a fifteen-pound weight loss for about one month. She had never been told that she had diabetes.

A large area of fluctuation near the heads of the first and second metatarsals was found on the dorsum of the foot. All the toes were cyanotic. No dorsalis pedis or posterior tibial pulses could be felt, but both popliteal arteries were palpable.

The diabetes was readily controlled with 30 units of NPH insulin. The patient was advised by the Surgical Service to have a midthigh amputation, but she refused. She was started on penicillin therapy, local drainage was begun, and wet soaks were applied. The second toe and distal phalanx of the great toe were amputated. The wound on the dorsum was closed by a skin graft with a 95 per cent take. The patient walked out of the hospital three months after admission.

Case 2. Mrs. W., a fifty-nine-year-old Negress, had diabetes three years previous to this hospital admission, controlled by 20 units of insulin. Her chief complaint was swelling of the left foot caused by slamming a door on it three days before.

Marked swelling of the entire foot was noted, as well as a hematoma on the dorsum on the foot, and the second toe was black. The dorsalis pedal and posterior tibial pulses were absent. The popliteal pulse was bounding.

The diabetes was regulated with 85 units of insulin daily. The patient was started on penicillin therapy. A left lumbar sympathectomy was done. The foot was debrided, and the second toe was amputated. The dorsum of the foot was skin-grafted with a good result. Complete healing occurred and the patient was discharged ten weeks after admission.

Case 3. Mr. R., a fifty-six-year-old man, was discovered to have diabetes seven years previously during an appendectomy. He had been advised to take 10 units of protamine zinc insulin daily but had discontinued it when urine tests for sugar were negative. Six years previous to admission he was hospitalized for diabetes (with no complications) and was again discharged on 10 units of protamine zinc insulin. Six days previous to this hospital admission he pared a corn on the fifth toe with a razor blade; following this the toe became painful and swollen and began to drain.

The fifth toe was swollen, red, and tender and was oozing pus; the entire foot was swollen, hot, and tender. The dorsalis pedal and posterior tibial pulses were not palpable. The diabetes was controlled with 35 units of protamine zinc insulin and 20 units of regular insulin. Penicillin therapy was started, and the fifth toe was debrided and dressed with wet packs.The cellulitis subsided gradually. A right lumbar sympathectomy was performed. The patient was discharged after two weeks of hospitalization. Two weeks later he returned because the fifth toe on the same foot was reinfected, necessitating its amputation. The infection had spread between the fascial planes. The dorsal and plantar surfaces of the foot were incised, necrotic tissue was removed, and the wounds were kept open. Subsequently, the wounds healed well, and the patient was discharged after three months of hospitalization.

Case 4. Mrs. P., a seventy-two-year-old widow, was admitted because of a sore right foot. She had diabetes of eighteen years' duration and was treated with 40 units of NPH insulin. Three years before, she had trimmed a callus of the left foot, with resultant cellulitis and gangrene; a midthigh amputation was performed. One month previous to this admission, blisters on the right foot developed as a result of ill-fitting shoes.

Physical examination showed that the second and third

toes on the right foot were black and dry, with redness of the surrounding tissues. No pedal or popliteal pulses were felt. A left sympathectomy was performed on Oct. 15, 1952. The second and third toes were amputated on November 5. The wound healed well and the patient was discharged on Dec. 14, after two months of hospitalization.

Case 5. Mrs. C., a sixty-nine-year-old woman, was admitted because of marked dyspnea. She had diabetes of six years' duration and had been taking 10 units of protamine zinc insulin daily. Two weeks previous to admission she noticed a "water blister" on the left toe, which she treated with potassium permanganate soaks and some type of powder.

On physical examination the temperature was 101° F., the pulse 130, and the blood pressure 180/108. There were rales at both lung bases, an enlarged heart, and a grade two apical systolic murmur. The left great toe was swollen, dark, and necrotic. The second and third toes were fissured and black with seropurulent discharge. The bone of the second toe was visible. Pedal pulses were absent. The diabetes was controlled on 10 units of NPH insulin daily. The cardiac failure was controlled with digitalis therapy. The second toe and metatarsal head and the distal phalanx of the first toe were excised. An incision was made along the entire plantar aspect of the foot for drainage. Saline soaks were administered. Slow healing took place and the patient was discharged Nov. 19, 1952. She was readmitted on December 10 with osteomyelitis of the remaining portion of the first toe, which cleared following ten days of penicillin therapy. Patient is limited by her cardiac status, but has a functional foot. She was discharged after three and a half months of hospitalization.

These few cases taken almost at random illustrate the need for prolonged hospitalization, the happy outcome of conservative therapy with early drainage of infected areas, and the great contribution of antibiotics to the saving of extremities.

SUMMARY AND CONCLUSION

Antibiotics, good diabetic management, and judicious surgery have revolutionized the management of foot lesions in diabetics. In dealing with infections, conservative treatment with frequent drainage of infected areas may necessitate prolonged hospitalization, but it is worthwhile if a major amputation can be prevented. Gangrene resulting from ischemia may respond to conservative treatment with minor amputations, but favorable results are not so striking as in cases with infection as the predominant factor.

The need for prolonged hospital treatment creates an increasingly large problem for service wards, and renders it imperative that city hospitals make provisions for the intelligent care of these patients by a well organized diabetes service.

ACKNOWLEDGMENTS

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Tractamento de Lesiones del Pedes in Diabete: Methodos Recommendate per le Servicio de Diabete al Hospital Municipal de Boston

Le tractamento de lesiones del pedes in diabeticos ha essite revolutionate per le advento del antibioticos, per meliorate therapias diabetic, e per le application judiciose de methodos chirurgic. In caso de infection, le tractamento conservative con un frequente drainage del area inficite require, il es ver, un prolongate hospitalisation, sed isto vale le pena si como resultato un major amputation pote esser evitate.

Gangrena resultante de ischemia pote responder a un tractamento conservative con minor amputationes, sed le favorabile resultatos assi obtenite non es tanto frappante como in le casos in que infection es le factor predominante.

Le requirimento de prolongate tractamentos hospitalari crea progressivemente plus serie problemas pro le salas de servicio general. Il es imperative que nostre hospitales municipal sia equipate a offerer a iste patientes un tractamento rational intra un ben-organisate servicio de diabete.

Causes of Chronic Disabilities in Diabetic Patients

Joseph I. Goodman, M.D., Cleveland Heights, Ohio*

The national mortality statistics in 1947 revealed that 37,515 persons died of diabetes, accounting for 2.6 per cent of all deaths and bringing diabetes into ninth position as a cause of death. While mortality statistics are important, they do not depict adequately the extent of the problem without consideration also of the disabilities of living patients.

In a recent report[1] dealing with 1219 patients admitted to a chronic disease hospital, the Cuyahoga County Nursing Home, the low rank of diabetes mellitus as a major cause of prolonged disability is worthy of note. In a specially selected subgroup of 431 patients in whom more accurate data were available, only two patients were admitted solely as a result of diabetic sequelae. Blindness due to retinitis proliferans was the cause of the disability in one patient, and diabetic nephropathy in the other. Other diabetic patients admitted to the institution were classified as to their principal disability and therefore not as diabetics primarily. Among these were 21, who had had amputation of a lower extremity necessitated by peripheral arteriosclerosis. The extremely low incidence of disability resulting directly from diabetes prompted further inquiry into the nature of the disorders which led to the hospitalization of these patients. The results of this study are reported herein.

Eighty-five, or 7.4 per cent, of 1219 patients admitted between 1939 and 1952 had diabetes mellitus. The ratio of females to males was greater than two to one. In a hospital population in which the incidence of chronic illness among Negroes is excessively high as compared to that of white persons, the incidence of diabetes is relatively even higher than the other chronic diseases. The age distribution of these hospitalized diabetics ranges from forty-nine to eighty-two years, with the largest numbers in the sixty to sixty-four and the seventy to seventy-four-year categories. With the exception of the latter peak, which I am at a loss to explain, the age distribution corresponds exactly to the mean ages of patients with other chronic illnesses. Patients admitted had had diabetes for thirteen years on the average, with a range of zero to thirty-one years' duration. Considering that one out of every six patients had newly discovered diabetes, the long duration of disease is even more striking in the remaining cases.

As can be seen in table 1, 58 per cent of the cases of disabilities fall into one of four categories: amputation due to peripheral arteriosclerosis, cerebral vascular accident, postencephalitic parkinsonism, and amyotrophic lateral sclerosis. The incidence of cerebral vascular accident and postencephalitic parkinsonism closely approximates the incidence in nondiabetic patients; in fact, patients with the former condition are even slightly less common in the diabetic population. For some unexplained reason, the number of diabetics with amyotrophic lateral sclerosis is disproportionately high as compared with the nondiabetics in this series of chronically ill patients.

TABLE 1

Causes of prolonged disability in 85 hospitalized diabetic patients

	No. of cases	Per cent
Diabetic retinopathy resulting in blindness	1	1
Diabetic nephropathy	1	1
Amputation resulting from peripheral arteriosclerosis	21	25
Cerebral vascular accident	14	16
Parkinson's syndrome	8	10
Amyotrophic lateral sclerosis	6	7
Other causes	34	40
Uremia, left ventricular failure, ischiorectal abscess and fistula, fractures, bone tuberculosis, mental deficiency, presenile dementia, malnutrition (severe), leg ulcer, traumatic, psychoneurosis, urinary incontinence.		

Amputation of one or both lower extremities, necessitated by gangrene secondary to peripheral atherosclerosis, is the leading cause of disability in this series, occurring in one out of four (25 per cent) of the diabetic patients. Apparently gangrene is much more im-

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portant as a chronic disability than as a reason for admission to acute hospitals, as can be seen from the following statistics. Gangrene was present in 3.8 per cent of all diabetic patients admitted to the New England Deaconess Hospital from 1939 to 1946, in 3.1 per cent of all diabetic admissions at the Mayo Clinic, and varies from 3.5 to 7 per cent in other hospitals in the United States. Relative to the present group it should be pointed out that these diabetics are culled from a chronic hospital population, and that gangrene is more common in patients over sixty years of age, the predominant age group in these patients.

Approximately 40 per cent of the diabetic patients in this study gave a history of definite symptoms of diabetes, principally polydipsia, polyuria, weight loss, and acidosis or coma. Sixty per cent of the cases either were overweight on admission or gave a previous history of obesity. One-half of the patients required a low caloric (reduction) diet, and of the remainder the majority were placed on a 2,200-calorie diet (isocaloric); a few required a 2,600-calorie diet (high caloric). One-third of the patients remained on insulin permanently. Eighty per cent of these patients were controlled most readily with two doses of regular insulin, the total daily dose per patient varying from 15 to 50 units. The remainder were controlled satisfactorily with a small dose (approximately 10 units daily) of globin insulin with zinc.

There were three other conditions in these diabetic patients which, although not usually a sufficient cause of permanent disability in themselves, are seen frequently and are deserving of mention, namely ocular manifestations, atherosclerosis, and neuropathy.

OCULAR MANIFESTATIONS

The two most important ophthalmologic lesions in this group of chronically disabled diabetic patients were cataract and retinopathy, each occurring in slightly less than one-third of the cases. Blindness resulted in three patients from these two conditions, in two from cataract, and in one from retinitis proliferans.

Corneal arcus was noted in one out of every five patients. Formerly considered a phenomenon of the aging process, arcus has recently been linked with disturbed cholesterol metabolism and atherosclerosis. A sluggish pupillary reaction to light was fairly frequent, occurring in approximately one-sixth of the diabetic patients. The best explanation of this pupillary abnormality is the autonomic nervous system involvement so frequently associated with diabetic neuropathy.

ARTERIOSCLEROSIS

The presence of advanced arteriosclerosis, either in the great vessels or the lower extremities, in 80 per cent of the diabetic patients in this study is in keeping with the previous findings of myself and others.[2-4] Generalized arteriosclerosis was demonstrable clinically in two-thirds of the patients, and coronary sclerosis in one-half. Some of the more valuable clinical signs for the detection of arteriosclerosis prior to the occurrence of thrombi might be mentioned. A palpable pulsation in one or both supraclavicular fossae was the most frequent physical sign, being noted in 75 per cent of the patients. Another excellent criterion of both proximal and coronary arteriosclerosis, when tested, is a cardiac standstill or a sustained drop in the systolic blood pressure with the carotid sinus pressure test.[5] A reduction in the oscillometric readings in the lower extremities was noted in 56 per cent of the cases, and in my experience this has proved to be the most valuable single indication of impaired peripheral blood flow.

Other well-known physical signs of peripheral occlusive vascular disease, namely diminished or absent pulses, atrophic skin and nail changes, rubor, pallor, etc., were inconsistent findings in these cases. The high incidence of ulcers, gangrene, and amputations in the lower extremities as a result of peripheral atherosclerosis has been alluded to.

NEUROPATHY

The very high incidence of peripheral nerve damage, noted in 70 per cent of the patients, only re-emphasizes our previous conclusions.[6] The most prominent neurologic findings, by far, are absent achilles tendon reflexes in 65 per cent of the patients and absent patellar reflexes in 34 per cent. Areflexia is much less common in the upper extremities. Although subjective symptoms occur far less commonly than areflexia, when they are present paresthesia and pain in the extremities are the most frequent ones. Objective neurologic findings, atrophy, hypesthesia, hypalgesia, and loss of position and vibratory sense occur only occasionally in diabetic neuropathy. Other manifestations of neuropathy encountered rarely are night cramps, chronic diarrhea, perforating ulcer, and elevated spinal fluid protein.

SUMMARY

Among 1,219 patients admitted to a chronic disease hospital, 7.4 per cent (85 patients) had diabetes, but in only two cases was the disability due solely to diabetes or its sequelae. One of these patients was admitted

because of blindness from retinitis proliferans, the other because of diabetic nephropathy.

In 25 per cent of the entire group of diabetics, the disability was due to amputation of an extremity resulting from peripheral arteriosclerosis, in 16 per cent to a cerebral vascular accident, in 10 per cent to one of the parkinsonian syndromes and in 7 per cent to amyotrophic lateral sclerosis. Nearly a dozen miscellaneous conditions were responsible for the disability in the remaining cases.

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SUMMARIO IN INTERLINGUA

Causas de Chronic Invaliditates in Patientes de Diabete

Inter 1.219 patientes admittite a un hospital de morbos chronic, il habeva 85 diabeticos (7,4 pro cento), sed le invaliditate de solo 2 de illes esseva exclusivemente le resultato de diabete o su consequentias. Un de iste patientes esseva admittite a causa de cecitate resultante de retinitis proliferante, le altere a causa de nephropathia diabetic.

In 25 pro cento del integre gruppo de diabeticos le invaliditate esseva le resultato del amputation de un extremitate in consequentia de arteriosclerosis peripheric; in 16 pro cento illo esseva le resultato de un accidente cerebrovascular; in 10 pro cento, de un accidente del syndrome parkinsonian; e in 7 pro cento, de sclerosis lateral amyotrophic. In le remanente casos le invaliditate esseva le resultato de alicun dece-duo conditiones miscellanee.

Detection of Chronic Disease in Los Angeles

A case-finding survey was conducted in the northeast health district of Los Angeles, in a 20-day period in March 1952. Screening tests were made for 3,203 persons, 23.3 per cent of the eligible population over 15 years. A total of 11,759 screening tests were made including chest X ray, blood sugar, hemoglobin and height-weight determinations. An analysis of the findings indicates that the survey may be credited with: six newly diagnosed cases of active tuberculosis, 1.8 per cent per 1,000 participants; 5 newly diagnosed "other pathology" such as emphysema, bronchiectasis, pleurisy; 16 newly diagnosed diabetics (6 per 1,000); 3 previously known diabetics returned to treatment; and 30 persons with abnormally low hemoglobins referred to clinic or private care (11 per 1,000); 1,073 (37.5 per cent) obese individuals informed as to significance of this situation and 90 (3.1 per cent) underweight persons advised to seek further examination.

From "Multiphasic Screening in a Health District of Los Angeles" by Stella B. Soroker, M.D., *Public Health Reports* 69:786-92, August 1954.

Blood-Sugar determinations

	Number	*Per cent*
Total screened	2,856	100.0
Technically unsatisfactory results	29	1.0
Total satisfactorily screened	2,827	100.0
Screened positive	87	3.1
Previously known diabetic	26	
Previously unknown diabetic	61	
Screened negative	2,740	96.9
Previously known diabetic	23	

Blood Sugar Recheck

	Number	*Per cent*
Total diabetes suspects	87	
Patients notified	87	100.0
Patients reporting	76	87.4
Number tests done	72	82.7
Previously unknown positives retested	55	
Retested positive (fasting and 2 hours post-sugar ingestion)	16	
Retest positive (2 hour post-sugar; negative fasting)	16	
Retested negative (fasting and 2 hours post-sugar)	23	
Previously known positives retested	17	
Retested positive (fasting only)	10	
Retested negative or under control (fasting only done)	6	
Retested technically unsatisfactory	1	

Summary

Total cases diabetes diagnosed	27	1.0
Previously unknown diabetics	16	.6
Previously known diabetics	11	.4

The Interrelationships of Exogenous Insulin and the Metabolism of Carbohydrate and Protein

Studies in Cases of Stable and Unstable Diabetes Mellitus

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Previous studies[1-3] showed that patients with diabetes mellitus could be separated into unstable and stable groups, on the basis both of clinical impression and of objective measures of the variability of blood and urinary sugar responses to different types of insulin. It was pointed out that these two clinical groups coincided with the two clinical types differentiated by Falta[4, 5] and by Himsworth[6, 7] on the basis of insulin-sensitivity tests. The unstable, insulin-deficient[4, 5] or insulin-sensitive type[6, 7] is seen mainly in the young but may occur at any age.[2, 8, 10] The stable, insulin-resistant[4, 5] or insulin-insensitive type[6, 7] is seen mainly in older individuals, especially obese females.

Bornstein and Lawrence[8] found no available insulin in the plasma of the first type following a carbohydrate meal, whereas the second type did contain insulin, approximately 70 per cent of that found in normal controls. Similarly, Wrenshall and his associates[9] were able to extract little or no insulin from the postmortem pancreases of the growth onset type of diabetes while the extractable insulin of the maturity onset type averaged about 50 per cent of normal controls. Bearn, Billing and Sherlock[10] associated the differences in general insulin sensitivity of the two types with differences in hepatic sensitivity to insulin. In the first or hepatic-sensitive type the fall in hepatic glucose output was greater than normal; in the second or hepatic-insensitive type the fall was less than normal. The recent report of Kirtley and collaborators[11] suggests that the differences in the two groups are not limited to differences in interplay between insulin and glucose. Glucagon produced a greater and more prolonged rise in blood sugar and a lesser fall in serum inorganic phosphate in stable than in unstable diabetes.

It is apparent that, depending on their specific method of approach, different investigators have used different terms to identify the same two groups. This may have led to some confusion in the literature. While no sharp line of demarcation may exist between the two types[2] and inconsistencies may be found with the use of any single criterion as the basis for separation,[12, 13] nevertheless the accumulating evidence from several different directions suggests that we may be dealing with two separate and distinct categories. We have continued to use the broad descriptive terms "unstable" and "stable" in designating the two types to point out what we consider is one of the salient differential features in their over-all clinical response.

For the past four years we have been conducting exploratory metabolic studies to evaluate different phases of metabolism in unstable and stable diabetics. The present report deals with certain aspects of the interrelationships of exogenous insulin and the metabolism of protein and carbohydrate in these two types.

EXPERIMENTAL DATA

Patients

Three representative patients with stable and three with unstable diabetes were selected for study in accordance with criteria set forth previously.[2] In order to reduce to a minimum the possible influence of such factors as age, duration of diabetes, and amount of exogenous insulin required, the patients were selected so that the two groups were roughly similar in respect to the factors

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mentioned. All were older individuals with diabetes of seven or more years' duration, taking between 30 and 60 units of insulin daily.

The case histories for each patient are summarized below with pertinent data presented in table 1.

CASE HISTORIES

Patient R. E. is a 59-year-old, moderately obese widow who has been followed regularly in the Diabetic Clinic since 1936. There has been a slow gradual weight loss over a period of several years from 102 to 78 kg., even though she has not always adhered to a diet of 1400 cal. (P 70 gm., F 70 gm., and C 125 gm.). Diabetes has been fairly well regulated on 25 to 40 units of insulin daily. Despite occasional mild to moderate postprandial hyperglycemia and glycosuria, there is no history of ketosis, symptoms of uncontrolled diabetes, coma or hypoglycemic reactions to insulin. The diabetes is complicated by peripheral arteriosclerotic vascular disease and diabetic retinopathy. The patient has been admitted several times in recent years for treatment of recurrent ulcers, cellulitis, and osteomyelitis of the feet. Several toes have been amputated.

Patient J. M. is a moderately obese 65-year-old married woman who has been followed regularly in the Diabetic Clinic since 1939. The diabetes has been fairly well regulated on a diet of 1500 cal. (P 66 gm., F 80 gm., and C 135 gm.) and 40 to 54 units of insulin daily. The weight has varied between 69 and 73 kg. (maximum ideal weight 54.1 kg.) for the past several years. Although moderate postprandial hyperglycemia and glycosuria have been noted on numerous occasions, usually in association with extra carbohydrate intake, there is no history of ketosis, symptoms of uncontrolled diabetes, acidosis, coma, or hypoglycemic reactions to insulin. The diabetes is complicated by arteriosclerotic heart disease with angina pectoris and by mild diabetic retinopathy.

Patient M. W. is a 78-year-old widow who has been followed regularly in the Diabetic Clinic since 1945. The diabetes has been fairly well regulated on a diet of 1800 cal. (P 76 gm., F 94 gm., and C 162 gm.) and 40 to 65 units of insulin daily. Her weight has ranged from 59 to 63 kg. Although moderate postprandial hyperglycemia and glycosuria have been noted, usually associated with ingestion of sweets, there is no history of ketosis, symptoms of uncontrolled diabetes, acidosis, coma, or hypoglycemic reactions to insulin. In fact, at one time the patient by mistake took 80 to 100 units of insulin for several months, instead of the prescribed 40 to 50 units without untoward effects. The diabetes is complicated by generalized arteriosclerosis, and arteriosclerotic heart disease, with auricular fibrillation, well-compensated on 0.1 gm. of digitalis daily. A few weeks prior to admission to the Metabolism Ward a localized cellulitis and osteomyelitis of the middle left toe developed following trivial trauma.

Patient M. S. is a 60-year-old married woman who has been followed regularly in the Diabetic Clinic since 1931. Her weight has been maintained consistently within normal limits on a diet of 1800 cal. (P 88 gm., F 81 gm., and C 181 gm.). For twenty years the daily insulin requirements have remained between 30 and 40 units. Despite careful regulation of diet and insulin the patient has never been able to avoid mild to moderate intermittent unpredictable glycosuria. She has always been markedly sensitive to insulin, reacting to slight excesses with a hypoglycemic shock for which she has required hospitalization on three different occasions. There is no history of acidosis or coma.

Patient G. M. is a 55-year-old married man who has been followed regularly in the Diabetic Clinic since 1947. He has had numerous admissions to the hospital for uncontrolled diabetes or hypoglycemic shock. The diabetes has been difficult to regulate, both in and out of the hospital. Although the patient has not always followed diet carefully, the weight has

TABLE 1

Supplementary information about the patients and diets used in this study

Patient	Age (yr.)	Sex	Duration of diabetes (yr.)	Height (cm.)	Type of body frame	Weight on admission (kg.)	Maximal ideal weight* (kg.)	Deviation from maximal ideal weight per cent	Insulin dose on admission units/day	Diet during hospitalization studies P gm.	F gm.	C gm.	calories Total
STABLE GROUP													
R.E.	59	F	25	162	large	76.8	64.1	+17	28	81	58	147	1,434
J.M.	65	F	17	154	medium	70.1	54.1	+23	45	78	65	153	1,511
M.W.	78	F	12	160	medium	62.0	58.2	+6	40	72	91	163	1,761
UNSTABLE GROUP													
M.S.	60	F	25	164	medium	61.1	60.9	0	30	88	82	187	1,838
G.M.	55	M	7	165	large	72.2	66.4	+8	60	98	98	222	2,169
F.H.	63	F	12	175	medium	55.5	68.2	−23	34	95	122	191	2,248

*Maximal ideal weights are taken from "Ideal Weight Tables Based on Maximum Longevity Derived from Statistics by the Metropolitan Life Insurance Company."[14,15]

been maintained consistently between 75 and 78 kg., on a diet of 2200 cal. (P 100 gm., F 100 gm., C 225 gm.). Insulin requirements have ranged from 60 to 90 units daily. The diabetes is complicated by chronic recurrent asthmatic bronchitis, hypertension, and hypertensive and arteriosclerotic heart disease with angina pectoris. On April 29, 1952, the patient was admitted to the hospital for treatment of asthma and mild ketoacidosis. On vigorous insulin and intravenous fluid therapy the ketosis, excessive hyperglycemia, and glycosuria cleared within four hours. Six days later the patient was transferred to the Metabolism Ward.

Patient F. H. is a 63-year-old married woman who has been followed periodically by private physicians since the discovery of her disease. The diabetes has been difficult to regulate despite good adherence to diet and various insulin regimens. Between 1945 and 1947, while on protamine zinc insulin the patient had frequent spells of impaired consciousness and bizarre behavior. The blackouts lasted from several minutes up to four hours or more and were more likely to occur at night. Because the spells were believed at first to be possible petit mal seizures by several consulting physicians, the patient was placed on anticonvulsive drugs by her private physician, but to no avail. Hospital studies in 1947 revealed that the spells were related to hypoglycemia. She was discharged on a diet of 2180 cal. (P 120 gm., F 100 gm., and C 200 gm.) and 50 units of globin insulin daily. The diabetes has continued to be difficult to regulate; sensitivity to insulin has fluctuated widely. Several weeks prior to admission to the Metabolism Ward the patient reduced her insulin from 50 to 34 units daily because of severe hypoglycemic reactions, coming on with little or no warning, usually in the late afternoon or early evening. On reduced dosage she developed marked glycosuria, polyuria, and polydipsia and lost 10 to 15 pounds. For several years her weight has been below the ideal weight.

Method of Study

Throughout the period of study, which in each case extended over several weeks, each patient lived quietly on the Metabolic Ward under carefully controlled uniform conditions. Activity was ordinarily restricted to being up and about on the floor.

Diets

Each patient received a chemically constant weighed diet throughout the study, the identical menu being served every day. All patients received four weighed meals daily, breakfast at 8:30 a.m., lunch at noon, supper at 5:00 p.m., and a small evening feeding at 9:30 p.m. The three unstable patients also received a small mid-afternoon feeding at 3:00 p.m. The details of the diets for the six patients are listed in table 1. The basic distribution of carbohydrate for the three meals was breakfast 20 to 25 per cent, lunch 30 to 35 per cent, supper 30 to 35 per cent, and in-between feedings 5 to 10 per cent.

In general, the diets approximated those that the patients were supposedly following at home. Patients R. E. and J. M. were on reducing diets; patients M. W., M. S., and G. M. were on diets calculated to maintain weight; patient F. H. was on a diet calculated to gain weight (see table 1). Although it was realized that this would result in somewhat uneven carbohydrate and caloric loads in the two groups, it was decided to perform the initial exploratory studies using the same dietary loads to which the patients supposedly had adjusted.

Insulin

Insulin was routinely administered to each patient as a single daily dose of NPH insulin. Initially the patients were placed on roughly the same dose of insulin that they had been receiving before hospitalization. Subsequently the dose was adjusted to achieve optimal regulation of blood and urinary sugar levels. In one of the unstable diabetics, patient F. H., a small supplementary dose of crystalline insulin before breakfast was added in order to achieve a more satisfactory regulation of the blood sugar levels. After several days of observation on what was considered optimal regulation for the patient, insulin was omitted altogether in the stable group for periods of 10 to 13 days, while in the unstable group it was reduced to 50 to 60 per cent of optimal levels for periods of six to ten days. In the latter group insulin could not be omitted altogether without rapid development of severe ketoacidosis.

Analytic Procedures

All the patients were weighed daily. Total fluid intake was maintained constant for each patient. Morning fasting blood sugars and twenty-four-hour urinary excretions of glucose and nitrogen were followed daily. Daily nitrogen balances were calculated from the observed daily urinary nitrogen and the average daily nitrogen in diet and stool. An identical sample of one day's diet was analyzed for nitrogen at least once during the period of observation. The average daily fecal nitrogen was obtained from a pooled stool collected for a five-day period. Carmine was given to mark the beginning and end of the stool collection.

Chemical Methods

Specimens of venous blood were analyzed for glucose according to Somogyi's modification of the Shaffer-Hartman copper iodometric method for "true" blood sugar estimation.[16, 17] Twenty-four-hour urines were analyzed quantitatively for glucose according to a modification of the Shaffer-Hartman method[18] using Somogyi's new copper reagent, and for total nitrogen by a modified micro-Kjeldahl method. Diets and stools were analyzed for nitrogen by the macro-Kjeldahl method using the wet technic.[19]

RESULTS

The metabolic data obtained for patients R. E., J. M., and M. W., with stable diabetes, are presented graphically in figures 1, 2, and 3; the actual laboratory and pertinent clinical data are illustrated by the summary given for J. M. in table 2. Similar data for patients M. S., G. M., and F. H., with unstable diabetes, are presented in figures 4, 5, and 6 and table 3 (patient G. M.).

ANALYSIS OF DATA

1. Stable Group

Carbohydrate Metabolism. As expected, the fasting blood sugar levels during the control period on optimal insulin therapy were maintained at normal or near-normal levels, without glycosuria or hypoglycemic reactions throughout the day (figures 1, 2, and 3 and table 2). Discontinuance of exogenous insulin for periods of ten to thirteen days uniformly resulted in a slow, smooth, gradual rise of the fasting blood sugars with a tendency

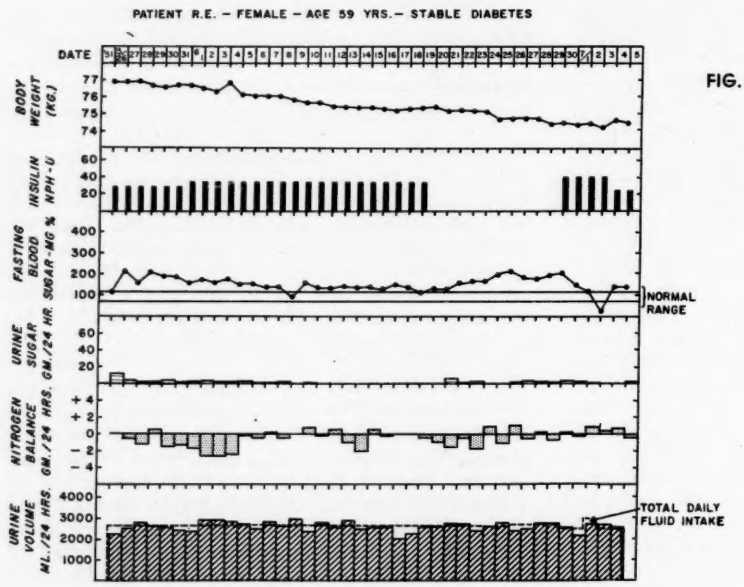

FIG. 1. Patient R. E., stable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to withdrawal of insulin for a ten-day period. For additional details see text.

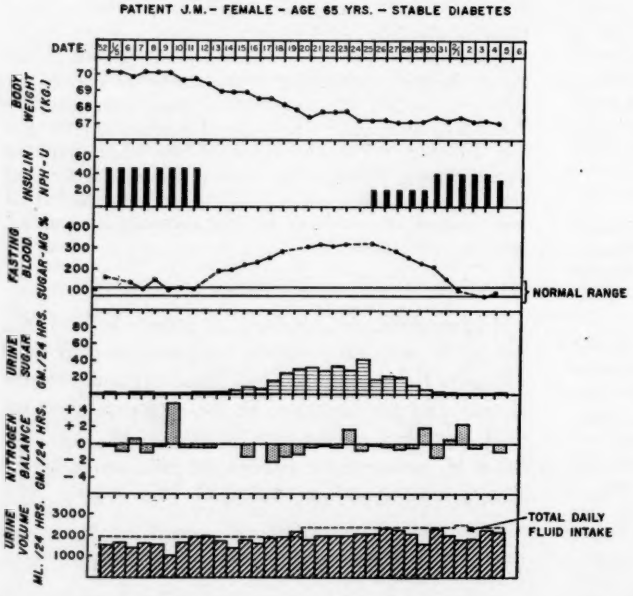

FIG. 2. Patient J. M., stable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to withdrawal of insulin for a thirteen-day period. For additional details see text and table 2.

to level off in the neighborhood of 200 mg. per cent in patient R. E. (figure 1) and 300 mg. per cent in patients J. M. (figure 2, table 2) and M. W. (figure 3). Patient R. E. remained essentially aglycosuric, whereas patients J. M. and M. W. gradually developed a moderate glycosuria up to 30 to 40 gm. daily. In both patients the glycosuria was accompanied by slight increases in urine output and mild thirst. Reinstitution of exogenous insulin therapy resulted in prompt clearance of the glycosuria and return of the blood sugar to previous levels. On the fourth day following reinstitution of exogenous insulin, patient R. E. developed severe hypoglycemia, necessitating a reduction in insulin. Note the absence of any so-called paradoxical rise in sugar

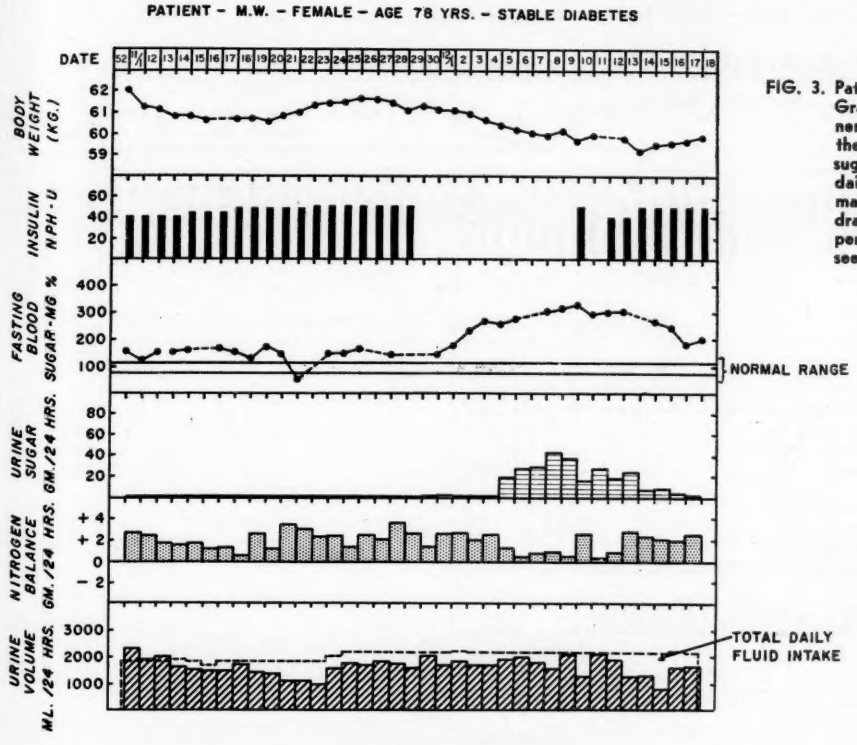
PATIENT – M.W. – FEMALE – AGE 78 YRS. – STABLE DIABETES
DATE
BODY WEIGHT (KG.)
INSULIN NPH-U
FASTING BLOOD SUGAR-MG %
NORMAL RANGE
URINE SUGAR GM./24 HRS.
NITROGEN BALANCE GM./24 HRS.
URINE VOLUME ML./24 HRS.
TOTAL DAILY FLUID INTAKE

FIG. 3. Patient M. W., stable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to withdrawal of insulin for a ten-day period. For additional details see text.

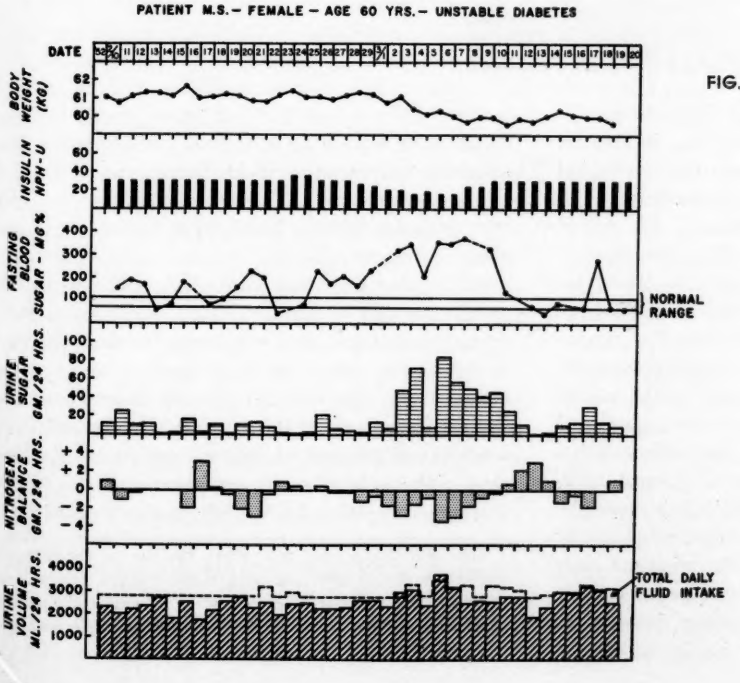

FIG. 4. Patient M. S., unstable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to reduction of insulin to suboptimal levels. For additional details see text.

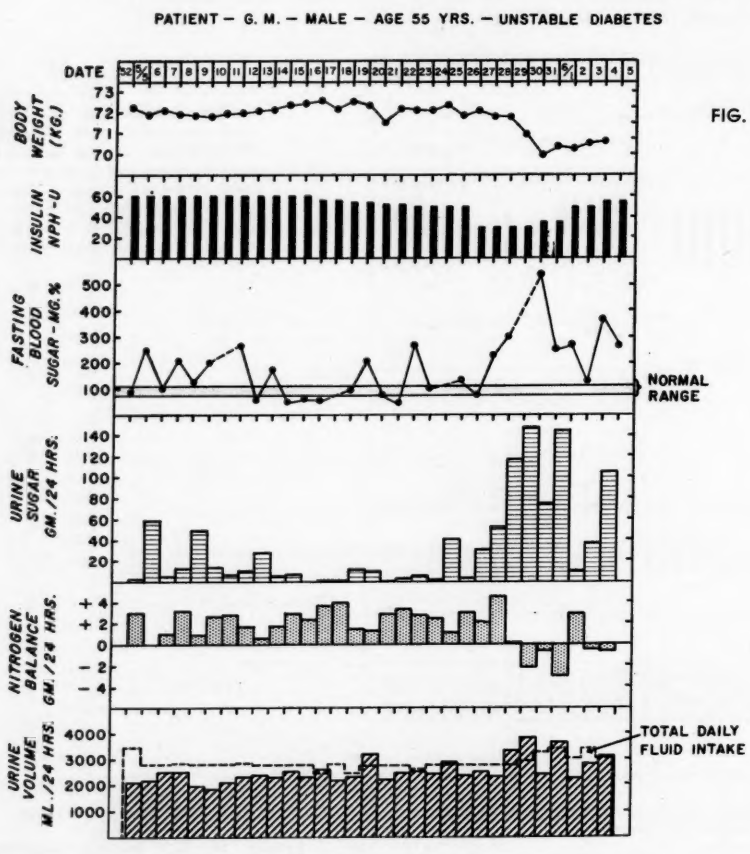
PATIENT — G. M. — MALE — AGE 55 YRS. — UNSTABLE DIABETES
DATE
BODY WEIGHT (KG.)
INSULIN NPH-U
FASTING BLOOD SUGAR - MG. %
NORMAL RANGE
URINE SUGAR GM./24 HRS.
NITROGEN BALANCE GM./24 HRS.
URINE VOLUME ML./24 HRS.
TOTAL DAILY FLUID INTAKE

FIG. 5. Patient G. M., unstable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to reduction of insulin to suboptimal levels. For additional details see text and table 3.

levels following the prolonged severe hypoglycemia.

Nitrogen Metabolism. Patient R. E. was in negative balance for nitrogen during the early part of the control period on optimal insulin therapy, approaching equilibrium about June 4 (figure 1.) Patient J. M. was in nitrogen equilibrium and patient M. W. in positive balance during the control periods. Discontinuance of insulin for ten days had little or no effect on the balance in patient R. E. In patient J. M. withdrawal of insulin for thirteen days was associated with a temporary negative balance for nitrogen. This appeared to be related to the rapid weight loss and not to the development of hyperglycemia and glycosuria. Note that with stabilization of the weight the patient returned to nitrogen equilibrium despite the increasing hyperglycemia and glycosuria. No significant correlation between either fasting blood sugar or amount of sugar in the urine and daily nitrogen balance was noted in the above patients (table 4). Patient M. W. remained in positive balance for nitrogen over the ten-day period of insulin withdrawal in spite of the weight loss and hyperglycemia and glycosuria. The delayed hyperglycemia and glycosuria were associated only with a slight fall in the amount of nitrogen retained daily. This accounts for the significant low correlation between blood sugar, urinary sugar, and urinary nitrogen (table 4).

On a sub-maintenance diet which was adequate in protein but low in purine* patient R. E. had a slow, gradual weight loss of 2.4 kg. over the forty-one days of observation, with a net loss of nitrogen of 22.40 gm. Patient J. M., who was also on a sub-maintenance diet, lost 3.1 kg. over the thirty-two days of observation with a net loss of nitrogen of only 6.3 gm. As noted above, most of the weight loss occurred over a ten-day period. The weight in patient M. W., who was on a maintenance

*The purine-free diet was given because of simultaneous studies on purine and uric acid metabolism, which will be reported separately. On June 30, toward the end of the studies, purines were reinstituted in the diet, which otherwise was unaltered.

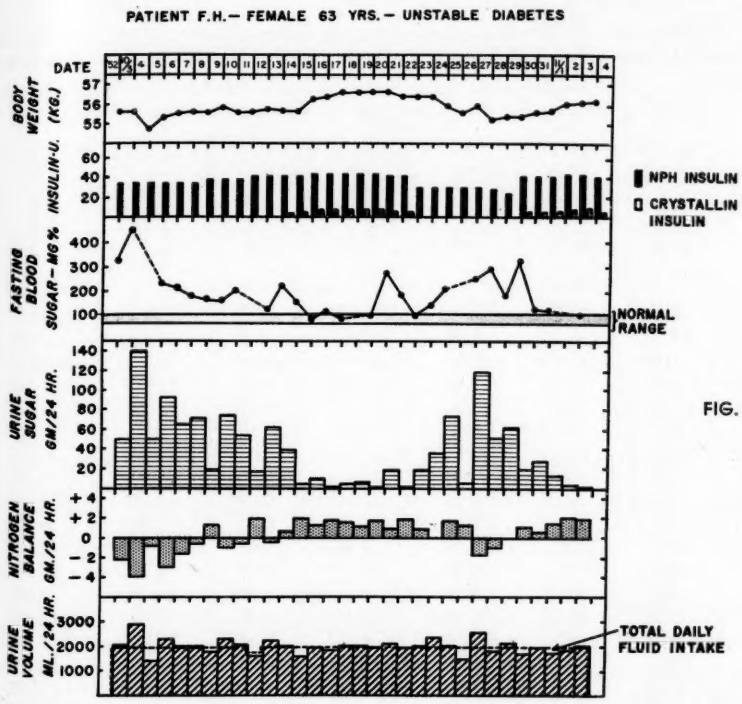

FIG. 6. Patient F. H., unstable diabetes. Graphic presentation of pertinent metabolic data showing the responses of the levels of sugar in blood and urine and the daily nitrogen balance to optimal insulin therapy and to reduction of insulin to suboptimal levels. For additional details see text.

diet, fluctuated throughout the study. During the control period there was an initial loss of body weight, followed by a stable period and a subsequent rise. On discontinuing insulin the weight again fell and then began to rise slightly on reinstituting insulin therapy. The weight changes were accompanied by a reciprocal rise and fall in the twenty-four-hour urine volume. Patient M. W. had a net gain of 69.73 gm. of nitrogen for the thirty-seven days of observation despite a net loss of 2.4 kg. in weight. It may be of interest to point out that the dietary history of this patient taken at the time of hospitalization revealed an adequate protein intake. However, a subsequent history suggested that perhaps the protein intake may possibly have been inadequate at times.

II. Unstable Group

Carbohydrate Metabolism. Figures 4, 5, and 6 and table 3 demonstrate the characteristic unstable responses of the blood and urinary sugar levels to optimal insulin therapy in the three patients with unstable diabetes as compared to the stable group. The instability of the levels of sugar in blood and urine may be noted not only with optimal insulin therapy but also with suboptimal therapy. This is particularly well demonstrated in patient F. H. (figure 6).

In all three patients reduction in insulin dose to 50 to 60 per cent of optimal was followed promptly by a progressive but irregular rise in blood and urinary sugar, increased urine output, ketonuria, negative water balance, and weight loss. By the third or fourth day the insulin dose had to be increased in patients M. S. and G. M. (table 3) because of symptoms of impending clinical acidosis. Both patients had negative water balance (as measured by intake and output), even though they were allowed to drink water freely during the period of reduced insulin dose. The reinstitution of insulin therapy at optimal doses was followed in all three patients by a prompt return of the blood and urinary sugar to or below previous levels. In two patients, M. S. (figure 4) and G. M. (figure 5), this was followed by a rebound or secondary rise in the sugar levels.

Nitrogen Metabolism. A high correlation between daily blood sugar, urinary sugar, and urinary nitrogen was noted in all three patients, both on optimal and suboptimal insulin therapy (table 4). There was a strong tendency for positive nitrogen balance to be associated with low sugar levels and vice versa. Reduction of the insulin dose to 50 to 60 per cent of optimal promptly resulted in negative nitrogen balance in each case. The degree of negativity was not always proportional to the

TABLE 2

Summary of metabolic and pertinent clinical data during period of balance studies in case J. M., stable type of diabetes. For additional details see text and figure 2.

Date	NPH Insulin u./day	Wt. (kg.)	Total fluid intake ml./day	Urine output ml./day	Fasting blood sugar (mg. %)	Urine sugar (gm./day)	Nitrogen intake (gm./day)	Nitrogen in feces (gm./day)	Nitrogen in urine (gm.)	Nitrogen balance (gm.)
1952										
1/5	45	70.1	1,890	1,535	160	1.66	12.44	0.94	11.86	−0.36
6	45	70.0	1,890	1,650	–	1.00	12.44	0.94	12.46	−0.96
7	45	69.8	1,890	1,410	133	0.78	12.44	0.94	10.87	+0.63
8	45	70.1	1,890	1,640	103	0.62	12.44	0.94	12.66	−1.16
9	45	70.1	1,890	1,570	145	0.57	12.44	0.94	11.88	−0.38
10	45	70.0	1,890	1,030	95	0.23	12.44	0.94	6.24	+5.26
11	45	69.6	1,890	1,680	108	0.55	12.44	0.94	12.03	−0.53
12	45	69.6	1,890	1,950	103	0.58	12.44	0.94	12.00	−0.50
13	0	69.3	1,890	2,000	–	0.93	12.44	0.94	12.00	−0.50
14	0	69.0	1,890	1,730	188	1.52	12.44	0.94	11.60	−0.10
15	0	68.9	1,890	1,400	192	4.31	12.44	0.94	11.63	−0.13
16	0	68.9	1,890	1,810	218	8.65	12.44	0.94	13.20	−1.70
17	0	68.5	1,890	1,620	235	6.29	12.44	0.94	11.44	+0.06
18	0	68.5	1,890	1,890	256	16.45	12.44	0.94	13.80	−2.30
19	0	68.1	1,890	1,920	282	25.30	12.44	0.94	13.07	−1.57
20	0	67.8	1,890	2,200	–	29.40	12.44	0.94	12.80	−1.30
21	0	67.4	2,390*	1,810	304	31.40	12.44	0.94	11.99	−0.49
22	0	67.7	2,390	1,980	320	26.50	12.44	0.94	11.83	−0.33
23	0	67.7	2,390	1,980	312	33.50	12.44	0.94	11.96	−0.46
24	0	67.7	2,390	1,980	321	27.90	12.44	0.94	9.93	+1.67
25	0	67.2	2,390	2,110	–	41.70	12.44	0.94	12.38	−0.88
26	20	67.2	2,390	2,100	325	16.65	12.44	0.94	11.75	−0.25
27	20	67.2	2,390	2,350	–	21.90	12.44	0.94	11.88	−0.38
28	20	67.1	2,390	2,260	290	20.90	12.44	0.94	12.27	−0.77
29	20	67.1	2,390	2,060	258	9.90	12.44	0.94	12.00	−0.50
30	20	67.1	2,390	1,615	227	5.58	12.44	0.94	9.68	+1.82
31	40	67.4	2,390	2,320	209	1.66	12.44	0.94	13.17	−1.67
2/1	40	67.2	2,390	2,040	158	0.91	12.44	0.94	10.95	+0.55
2	40	67.4	2,490	1,810	101	0.51	12.44	0.94	9.15	+2.35
3	40	67.1	2,390	1,850	–	0.56	12.44	0.94	12.03	−0.53
4	40	67.2	2,390	2,310	74	0.39	12.44	0.94	11.40	+0.10
5	32	67.0	2,390	2,170	91	0.60	12.44	0.94	12.49	−0.99

*Complaining of slight thirst. 500 ml. of water added to fluid intake.

degree of glycosuria. On reinstitution of optimal doses of insulin the balances promptly reverted to positive. In patients M. S. and G. M. this was followed by a return to temporary negative balance simultaneous with the rebound or secondary rise in blood and urinary sugar.

On optimal doses of exogenous insulin, patients G. M. and F. H. maintained positive daily balances for nitrogen. Note the lack of correlations between caloric load or weight changes and nitrogen retention in these two patients. Patient G. M., who was on a maintenance diet, had a net positive balance of 46.96 gm. with a net weight loss of .4 kg. during the twenty-two-day control period of optimal insulin therapy (figure 5). Patient F. H., who was on a super-maintenance diet, had a net positive balance of 11.80 gm. of nitrogen with a weight gain of 0.7 kg. during the eight-day period of optimal insulin therapy (figure 6). In both cases the degree of positivity varied in accordance with the changes in levels of sugar in blood and urine; the higher the levels the lower the nitrogen retention and vice versa. As a rule, the maximal retention of nitrogen was associated with the lowest levels of blood and urine sugar. In patient

TABLE 3

Summary of metabolic and pertinent clinical data during period of metabolic studies. Case G. M., unstable type of diabetes. For additional details see text and figure 5.

Date	NPH Insulin u./day	Wt. (kg.)	Total fluid intake ml./day	Urine output ml./day	Fasting blood sugar (mg. %)	Urine sugar (gm./day)	Nitrogen intake (gm./day)	Nitrogen in feces (gm./day)	Nitrogen in urine (gm.)	Nitrogen balance (gm.)	Comments
1952											
5/5	60	72.2	3,450	2,100	87	1.42	16.20	0.92	12.40	+2.88	
6	60	71.0	2,750	2,190	248	57.70	16.20	0.92	15.26	+0.02	
7	60	72.1	2,750	2,498	100	4.40	16.20	0.92	14.25	+1.03	
8	60	71.9	2,850	2,500	210	12.10	16.20	0.92	12.15	+3.13	
9	60	71.8	2,750	1,910	119	48.90	16.20	0.92	14.43	+0.85	
10	60	71.8	2,750	1,855	200	13.18	16.20	0.92	12.58	+2.70	
11	60	71.9	2,750	2,095	—	7.20	16.20	0.92	13.55	+1.73	
12	60	72.0	2,850	2,270	267	11.25	16.20	0.92	13.65	+1.63	
13	60	72.1	2,750	2,345	75	28.30	16.20	0.92	14.60	+0.68	
14	60	72.2	2,750	2,270	171	5.60	16.20	0.92	13.55	+1.73	
15	60	72.3	2,750	2,500	46	6.20	16.20	0.92	12.38	+2.90	
16	60	72.4	2,750	2,310	58	0.23	16.20	0.92	13.00	+2.28	
17	56	72.6	2,450	2,590	55	0.98	16.20	0.92	11.65	+3.63	
18	56	72.2	2,850	2,160	—	0.88	16.20	0.92	11.43	+3.85	Hypoglycemic reaction before & after supper. 100 g. O.J. 7 p.m.
19	54	72.5	2,450	2,320	94	11.11	16.20	0.92	13.87	+1.41	
20	54	72.4	2,750	3,210	211	9.35	16.20	0.92	14.10	+1.18	
21	52	71.5	2,750	2,150	74	1.15	16.20	0.92	12.47	+2.81	
22	52	72.1	2,750	2,440	44	2.66	16.20	0.92	12.05	+3.23	Hypoglycemic reaction 2:30 p.m. 100 g. O.J.
23	50	72.1	2,575	2,510	270	5.39	16.20	0.92	12.53	+2.75	
24	50	72.1	2,750	2,400	99	1.88	16.20	0.92	12.85	+2.43	
25	50	72.4	2,750	2,860	—	41.00	16.20	0.92	14.15	+1.13	
26	50	71.8	2,750	2,350	133	2.66	16.20	0.92	12.30	+2.98	
27	30	72.1	2,750	2,510	69	30.70	16.20	0.92	13.15	+2.13	
28	30	71.8	2,750	2,320	228	52.60	16.20	0.92	10.73	+4.55	
29	30	71.8	2,750	3,365	305	116.90	16.20	0.92	15.15	+0.13	Acetone but no diacetic in urine.
30	30	71.0	2,900	3,850	—	147.20	16.20	0.92	17.59	−2.31	Asthma. Acetone +; diacetic −0.
31	35 +20*	70.0	3,260	2,350	540	74.20	16.20	0.92	15.90	−0.62	Asthma, nauseated, weak, sl. drowzy. Acetone 4+, diacetic + in a.m. 15 u. CI at noon and 5 u. at supper.
6/1	35	70.4	3,400	3,640	255	144.90	16.20	0.92	18.17	−2.89	Feeling better, alert, no acetone or diacetic.
2	50	70.2	3,010	2,240	264	10.65	16.20	0.92	12.38	+2.90	No complaints.
3	50	70.5	3,400	2,825	126	37.10	16.20	0.92	15.69	−0.41	
4	55	70.6	3,025	3,100	364	104.50	16.20	0.92	16.02	−0.74	Trace acetone in 24 hr. urine.
5	55	—	—	—	263	—	—	—	—	—	

*Cryst. Insulin

M. S. negative daily nitrogen balances were associated with even relatively mild waves of hyperglycemia and glycosuria (less than 20 gm.).

DISCUSSION

Under the conditions of this study the stable group appeared to differ from the unstable group in two major respects: first, patterns of response to withdrawal or suboptimal levels of insulin therapy; second, interrelationships of protein and carbohydrate metabolism. It should be emphasized at the outset that the observed differences in behavior between the two types of diabetes which have been studied are not considered as adequate proof of a fundamental metabolic difference between them. The interpretation of the differences is complicated by the fact that the diets in the two groups were somewhat different, particularly in respect to carbohydrate and total caloric content. The rationale for the

TABLE 4

Coefficients of correlation between a) fasting blood sugar and 24-hour urine sugar; b) fasting blood sugar and 24-hour urine nitrogen, and; c) sugar and nitrogen in 24-hour urine in three patients with stable and three with unstable types of diabetes mellitus

Patient	Stability of carbohydrate metabolism	a	b	c
R.E.	Stable	.036	.080	.100
J.M.	Stable	.877**	.262	.207
M.W.	Stable	.799**	.492**	.507**
M.S.	Unstable	.778**	.605**	.586**
G.M.	Unstable	.584**	.428*	.752**
F.H.	Unstable	.612**	.637**	.921**

*Significant at the 5 per cent level.
**Significant at the 1 per cent level.

use of the particular diets chosen in these initial studies has already been discussed. Furthermore, the limited number of cases in each group does not preclude the possibility of chance differences in the behavior of the two groups on insulin withdrawal. Nevertheless, there are certain features in the behavior of the two groups which at least suggest the possibility of a difference in the interrelationships of carbohydrate and protein metabolism in the two types. These deserve comment.

Prior to discussing the behavior of the two groups it may be worthwhile to comment briefly on the instability of the sugar levels in blood and urine in the unstable group. This has been attributed by some[20-23] to over-energetic attempts to maintain normal levels, resulting in frequent hypoglycemia followed by anti-insulin adjustments and rebound in blood sugar level, so-called "paradoxical hyperglycemia." While attempts to maintain normal sugar levels may exaggerate the unstable response, the present as well as extensive earlier studies[1-3] indicate that level of regulation is not the limiting factor. The smooth, flat, predictable response of the stable group at almost any desired level of glycemia and glycosuria stands out in sharp contrast to the uneven, unpredictable response of the unstable group. The mechanisms involved remain to be clarified.

Despite the similarity in range of insulin requirements of the two groups, the unstable group appeared to be much more dependent upon exogenous insulin than the stable group. Much greater degrees of glycosuria were produced in the unstable group on reduction of the dose of insulin than in the stable group on withdrawal of insulin. In the former the increasing glycosuria was associated with prompt but variable loss of body nitrogen irrespective of the state of the over-all nitrogen balance prior to reduction of the dose of insulin, one of the patients being in equilibrium and two in positive balance prior to the reduction. In contrast, negative nitrogen balances did not develop in any of the unstable group on insulin withdrawal. In only one patient (M. W.) did insulin withdrawal have any effect on the nitrogen balance. In this patient, who maintained a positive balance for nitrogen throughout the entire period of study, the glycosuria which followed the withdrawal of insulin was accompanied only by a slight depression in the positivity of the nitrogen balance.

It is pertinent at this point to inquire what role, if any, the somewhat unequal carbohydrate and caloric loads of the two groups played in the observed differences. These exploratory studies do not provide a conclusive answer. However, we doubt that the differences in diet can explain all of the observed differences, especially in view of the consistency of response within each group despite intra-group variation in carbohydrate and caloric loads, over-all nitrogen balance, and exogenous insulin requirements. The response to insulin withdrawal in all three stable patients was fairly uniform, although two of the patients (R. E. and J.M.) who were on sub-maintenance diets lost weight, while the third patient (M. W.), who was on a maintenance diet, did not lose weight during the control period and in addition had a localized infection of her toe. Furthermore, the responses of M. W., a stable diabetic, and G. M., an unstable diabetic, were strikingly different even though on maintenance diets and optimal insulin therapy both patients were in positive nitrogen balance without losing or gaining weight. Studies are in progress to evaluate more thoroughly the influence of diet changes on the observed differences in behavior of the two groups.

Of considerable theoretical as well as practical interest is the statistically significant correlation between the daily levels of sugar in blood and urine and the daily nitrogen balance in each of the unstable patients irrespective of the over-all status of nitrogen balance—that is, positive, negative, or in equilibrium—and of the level of insulin therapy—optimal or suboptimal. It was surprising to find that relatively mild to moderate degrees of glycosuria were associated with subtle but nevertheless significant changes in nitrogen retention. Even though the over-all nitrogen balance was positive, the daily amount of nitrogen retained appeared to be influenced by the daily levels of sugar in blood and urine.

Excessive protein catabolism in uncontrolled severe diabetes is well known. Wilder[24] was perhaps the first

to demonstrate the promptness with which azoturia can develop in severe diabetes after the period of activity of a preceding dose of insulin. A continuous supply of insulin was necessary to prevent intervals of azoturia and creatinuria during a twenty-four-hour period. Short-term balance studies in two cases revealed that such periodic intervals of azoturia were not encountered when an insulin was used which had an activity extending beyond twenty-four hours even though the amount of insulin was insufficient to control the postprandial glycosuria. The present more extensive studies indicate an even closer relationship between carbohydrate and protein metabolism in unstable diabetes. In fact, the significant positive correlation between the daily levels of glucose in blood and urine and the daily levels of nitrogen in the urine in the unstable group suggests that the instability of the carbohydrate metabolism is paralleled by a corresponding instability of the protein metabolism. Furthermore, the seemingly disproportionate degree of sensitivity of the relationship raises the possibility that the parallelism is not necessarily one of cause and effect but a reflection of a simultaneous but independent influence of insulin on protein and carbohydrate metabolism. This would be in accord with experimental studies[25,26] suggesting that insulin action on protein synthesis may be a primary influence rather than a secondary one following its priming of glucose metabolism.

Recent experimental studies in animals on the importance of insulin in nitrogen retention and growth receive clinical support from the present studies. Milman, DeMoor, and Lukens[27] showed that the administration of growth hormone to a depancreatectomized cat caused no anabolism of protein unless insulin was given simultaneously, and the retention of nitrogen induced by growth hormone was not maximal unless a substantial dose of insulin was given in addition to that needed by the animal in the absence of growth hormone. Salter and Best[28] have reported increases in weight, body protein, and skeletal size in hypophysectomized rats given small doses of a long-acting insulin. This was associated with increased appetite and food intake as compared to the hypophysectomized controls. The role of increased food consumption was not evaluated. Although the present studies are not exactly analogous to the experimental studies cited, it is of interest that especially in the unstable group the amount of nitrogen retained tended to be inversely proportional to the levels of sugar in blood and urine. As a rule the maximal retention of nitrogen appeared to be associated with the lowest sugar levels. Furthermore, the nitrogen retained was independent of changes in body weight. A positive balance was seen not only with increase in body weight but also with no change or even a decrease.

It would seem reasonable to conclude from this that changes in body fat were balancing the nitrogen retention. In other words, nitrogen was retained at the expense of body fat. In view of the importance of fat as a metabolic pathway for carbohydrate and its possible importance as a source of glucose, more information on the possible interrelationships of fat metabolism and the observed deviations of carbohydrate and protein metabolism would be pertinent. The practical implications of the observed interrelationships seem self-evident.

According to Bornstein's[8] and Wrenshall's[9] studies, one would expect the totally insulin-deficient, anti-insulin type of patient to require more insulin than the stable, only partially deficient patient. In fact, however, the unstable group required about the same—or even less—insulin than the stable insulin-independent group. This is particularly impressive in view of the somewhat higher carbohydrate and caloric load of the unstable group and would be difficult to explain purely on the basis of quantitative differences in the deficiency of endogenous insulin. These discrepancies as well as the striking differences in the metabolic responses of the two groups to exogenous insulin suggest that other factors may be involved.

SUMMARY

The interrelationships of exogenous insulin and the metabolism of protein and carbohydrate were studied in three patients with stable and three with unstable diabetes by following the responses of the daily levels of sugar in blood and urine and the daily nitrogen balances to optimal doses of insulin as well as suboptimal doses or withdrawal of insulin. The two groups were similar in age, duration of diabetes, and amount of exogenous insulin required. The diet used in each patient corresponded roughly to that which the patient previously had been receiving prior to the study. In the stable group two were on sub-maintenance diets and one was on a maintenance diet, while in the unstable group two were on maintenance diets and one on a super-maintenance diet.

Under the conditions of this study the two groups differed in two major respects: first, patterns of response to withdrawal of or to suboptimal levels of insulin therapy; second, interrelationships of daily sugar levels and nitrogen balances.

In the stable group discontinuance of exogenous insulin for periods of ten to thirteen days resulted in the

delayed gradual development of relatively constant hyperglycemia and glycosuria of mild to moderate degree without associated ketosis or negative nitrogen balance. No significant correlation between the levels of sugar in blood or urine and the daily nitrogen balance was noted in two patients. In the third patient, who maintained a positive balance for nitrogen throughout the study, the hyperglycemia and glycosuria which followed the withdrawal of insulin were associated only with a small but significant depression in the positivity of the balance.

In contrast, merely reducing the dose of exogenous insulin to 50 to 60 per cent of optimal in the unstable group resulted in prompt, progressively severe but irregular hyperglycemia and glycosuria, negative balances for nitrogen and water, ketonuria, and weight loss. A significant positive correlation between the daily sugar levels and the urinary excretion of nitrogen was noted in each patient irrespective of the over-all status of nitrogen balance—that is, positive, negative, or in equilibrium—and of the level of insulin therapy, optimal or suboptimal. This suggests that the instability of the sugar levels is paralleled by a corresponding instability of the nitrogen balance. There was a definite tendency for low sugar levels to be associated with positive nitrogen balances and vice versa. In general, the maximal retention of nitrogen tended to be associated with the lowest sugar levels. The nitrogen retained appeared to be independent of changes in body weight.

The findings of the study suggest that the interrelationships of carbohydrate and protein metabolism may be defined separately for each of the two groups, notwithstanding some variation in the caloric and carbohydrate loads in the cases discussed. It remains for future studies to establish whether the results can be explained on the basis of quantitative differences in the available endogenous insulin in the two groups, or whether other factors are involved.

The results also appear to lend clinical support to recent experimental observations which suggest that insulin may be important not only in preventing protein breakdown, but in promoting nitrogen retention and, presumably, protein synthesis.

DISCUSSION

JOSEPH L. IZZO, M.D., (*Rochester, New York*): The only thing I may add is that I hope this small study will serve to stimulate interest in a study of other phases of metabolism in these two groups. We may find where there are common areas of disturbances, and where there are differences. It is possible that we may achieve by this approach some knowledge about the complications and even about the mechanisms of diabetes itself.

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SUMMARIO IN INTERLINGUA

Le Interrelation de Insulina Exogene con le Metabolismo de Hydrato de Carbon e Proteina. Studios in Casos de Stabile e Instabile Diabete Mellite

Esseva studiate le relation inter insulina exogene e le metabolismo de proteina e hydrato de carbon in tres casos de stabile diabete e in tres casos de instabile diabete. Le methodo usate consisteva in observar le responsa del nivellos diurne de sucro in sanguine e urina e del balancia diurne de nitrogeno a (1) dosages optimal de insulina, (2) dosages suboptimal de insulina, e (3) abstention de insulina. Sub le conditiones de iste studio le duo gruppos differeva in duo respectos principal, i.e., (1) in lor responsa al abstention o al administration de dosages suboptimal de insulina e (2) in le interrelation de lor nivellos diurne de sucro a lor balancias diurne de nitrogeno.

In le gruppo de stabile diabeticos le cessation del administration de insulina exogene pro periodos de inter dece e dece-tres dies resultava in un retardate disveloppamento gradual de relativemente constante hyperglycemia e glycosuria de leve o moderate grados sin associate cetosis o negative balancia de nitrogeno. Del altere latere, in le gruppo de instabile diabeticos le mer reduction del dosages de insulina exogene a inter 50 e 60 pro cento del valores optimal resultava in le prompte apparition de sever sed irregular hyperglycemia e glycosuria, negative balancias de nitrogeno e aqua, cetonuria, e perdita de peso.

Le constatationes indica que le interrelation del metabolismos de hydrato de carbon e de proteina differe in le duo gruppos de diabeticos. Le constatationes etiam pare corrobar le recente observationes experimental ab le quales on ha concludite que insulina es importante non solo in prevenir le catabolismo de proteina sed etiam in promover le retention de nitrogeno e possibilemente le synthese de proteina.

Inheritance and Anticipation in Diabetes Mellitus in Relation to Carbohydrate Metabolism During Pregnancy

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In a recent splendid review and synthesis of the literature on carbohydrate metabolism during pregnancy, Hoet[1] underscored the effects of pregnancy on prediabetic and diabetic women and their offspring. He partially summarized his evaluation of his own data as well as those published by others as follows:

"1. In patients with a diabetic trait or with latent weakness of insulin production, pregnancies provoke a disturbance in the regulation of carbohydrate metabolism, as evidenced by the hyperglycemic tolerance curve.

"2. It appears that the transitory diabetes which occurs at each pregnancy is transformed by such repetition into permanent diabetes.

"3. The fetal loss rate progresses from 20 to 50 per cent in proportion to the increasing severity of the disordered glucose metabolism. A large number of the infants who are born alive have an excessive weight . . . .

"4. The tendency to obesity, hyperglycemia, and finally diabetes which characterizes the ultimate development of a great number of these infants are the consequence, on the one hand, of heredity and, on the other hand, of the maternal environment of *milieu intérieur* at the time of embryonal development."

Hoet offers methods to prevent the undesirable consequences of the stress of pregnancy on carbohydrate metabolism.

Physicians will want to examine the clinical aspects of Hoet's conclusions. Geneticists will be concerned with the implications of his conclusions concerning the genetics of diabetes and the so-called phenomenon of "anticipation."

As a geneticist, I am interested in the latter problems. I should like to discuss Hoet's theses as they pertain to the expression of diabetes, first in the mother and then in the offspring of prediabetic and diabetic women.

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PREGNANCY AND THE EXPRESSION OF DIABETES IN THE MOTHER

Hoet's view that pregnancy may precipitate diabetes in a woman genetically predisposed to the disease is, in principle, in accord with many well-known instances in the literature in which the expression of a gene-determined character is conditioned by variations in the environment.

Geneticists have long recognized that the expression of a genetically determined character is never independent of its environment, internal as well as external. In general, we may say that all genes require a suitable environment to function and that the effect resulting from the action of a gene or genes (the phenotype) may be modified by proper manipulation of the environment. The method of doing this is not always obvious, and indeed, in some instances, we know of no way of doing this short of killing the organism. The blood types of man and other animals are an excellent example of genetically determined characters whose expression has thus far defied all efforts to change them.

At the other extreme are characters so sensitive to variations in the environment that it has been impossible to stabilize them even after many generations of inbreeding. An example is the phenotype of mice homozygous for the recessive mutation "myelencephalic blebs."[2] Despite many generations of inbreeding, mice homozygous for this mutation may show no abnormalities at all, or they may have abnormalities of the eyes, feet, or coat or combinations of these. The abnormalities shown by these structures vary widely. According to Bonnevie[3] and others, these defects result from the pressure exerted by blebs in the regions in which they come to rest.

Most gene-determined characters lie between these extreme types. It is the intermediate types that are of most interest, because the expression of diabetes with regard to age at onset and severity seems to be sensitive to environmental changes, and because the tendency to diabetes appears to be gene-determined.[4]

Many different types of variation of the environment

have been shown to affect the expression of genes. The mutant gene called Danforth shorttail (symbol Sd) leads, in heterozygous mice (Sd sd), to a reduction of the tail to one-eighth or less of the normal tail length.[5] Mice homozygous for this gene (Sd Sd) are born tailless, with an imperforate anus and no genital papilla. They die within twenty four hours after birth. In the stock in which the mutation was first described all homozygotes regularly lacked both kidneys. The majority of the heterozygotes had kidneys which were smaller than normal. Crosses of the original strain to various other strains modified the expression of the gene in both homozygotes and heterozygotes. In some crosses none of the heterozygotes had detectable kidney changes, while the homozygotes had various grades of reduction ranging from a slight reduction of the kidneys to complete absence of the kidneys and the ureters.[6] No effect on the imperforate anus has been observed.

In man the erythrocytes of individuals with the sickle cell trait (heterozygous for the sickle-cell gene [Si si]) can be caused to sickle in reduced oxygen atmospheres. These individuals have no clinical complaints. Similarly, individuals with Cooley's trait (heterozygous for the gene which when homozygous leads to Cooley's anemia) have no clinical complaints. They may be recognized by the presence of oval erythrocytes, target cells, decreased red blood cell size, decreased fragility of the erythrocytes in hypotonic saline, and so on.[7]

Individuals heterozygous for both these genes (Si si, Co co) suffer a chronic hemolytic anemia clinically indistinguishable from sickle-cell disease. Electrophoretic studies of the hemoglobin show, however, that individuals with "true" sickle cell disease do not have fetal hemoglobin, while those whose disease is due to the interaction of the sickling and Cooley's trait genes do.[8-10]

The foregoing are illustrations of the modifications of the effects of genes by other genes. Let us now consider some examples of the interaction of a gene or genes with the nongenetic environment.

Rabbits homozygous for a certain recessive gene lack the enzyme which converts ingested xanthophyll into a colorless substance.[11] Accordingly, such animals have yellow fat rather than the white fat of normal rabbits. When, however, such rabbits are fed a xanthophyll-free diet, their fat is white and is indistinguishable from normal fat.

A not very dissimilar illustration may be taken from man. There is considerable evidence that susceptibility to hay fever is genetically determined. If an individual susceptible to ragweed pollen is never exposed to it, he suffers no hay fever and cannot readily be distinguished from individuals who do not form antibodies to ragweed pollen proteins.

It is well-known that several inbred strains of mice develop cancer spontaneously. Work with some of these strains is of particular interest for our present purposes. In one strain almost 100 per cent of the mice develop lung tumors at an average age of about twenty months. When young animals from this strain are treated with a tumorigenic agent they develop tumors at an earlier age than when they are not so treated. In addition, the tumors show many more foci than when no treatment is used. Animals from the strains which do not develop lung tumors spontaneously will also develop lung tumors when treated with a tumorigenic agent, but the tumors develop a longer time after treatment and show fewer foci.[12] Both types of mouse strain respond to the tumorigenic agent, but the strain that is genetically predisposed to tumor formation does so more readily and more vigorously.

A more striking parallel to what Hoet describes for the role of pregnancy in the prediabetic woman may be derived from a consideration of some strains of mice in which a large proportion of the females develop mammary carcinoma spontaneously. It has been demonstrated for some of these strains that litter bearing increases the probability of the animal's developing breast cancer.[13]

These few illustrations, chosen from a great many that are known, should suffice to demonstrate that geneticists have for a long time been aware that the environment, internal as well as external, may enhance or suppress the expression of a genetically determined character. The direction and magnitude of the effect depend on the character and the environmental variation under consideration. Hoet's suggestion that pregnancy may precipitate diabetes in a woman who is genetically predisposed to the disease is, therefore, in complete agreement with known genetic experience and, consequently, is readily acceptable to the geneticist. From the geneticist's point of view, the problem is not "Is this a possible or probable event?" but rather "What will be the observed effect on genetic ratios if the phenomenon occurs?" and "What data do we need to detect the effect?"

It is, of course, well-known that factors other than pregnancy, such as overeating, infections, or emotional stress, are believed to precipitate diabetes in susceptible individuals. If these factors are of more frequent occurrence than pregnancy as causes of frank diabetes, or if these factors do not occur with equal frequency among

women with children, childless women, and men, the effects of pregnancy as a cause of frank diabetes may be obscured when studied from a statistical viewpoint. On the other hand, if pregnancy is a relatively frequent precipitant of diabetes in prediabetic women, we might expect certain events to follow:

1. Diabetes should be more frequent among women with children than among childless women or men.

2. The age-specific incidence for diabetes after age thirty should be greater among women with children than it is among childless women or men.

Munro, Eaton, and Glen[14] attempted to determine by statistical means the effects of pregnancy on the prevalence and characteristics of diabetes. They found no correlation between the age at onset or severity of diabetes and childbearing among women forty-five years or older at the time of onset of diabetes. A much higher proportion of the diabetic women who developed diabetes after age forty-four had large families than did hospital visitors of similar age. This observation may, however, be an artifact because hospital visitors may well have fewer children than women in the general population. It is easier for women with few children to visit a hospital than it is for women with many children. It is unfortunate that the authors did not compare their values with those for the general population and with those for other hospital patients.

In the hospital sample examined by Munro and his colleagues, the age-specific prevalence of diabetes among individuals more than thirty-four years of age was much greater among married women than among single women or men. This difference was particularly striking among those forty-five years or older at the time of the study. This observation also may not be taken at face value because a hospital population is not necessarily (indeed is not likely to be) representative of the population at large. One must consider such factors as the comparative probabilities of diabetes being diagnosed in an affected man, an unmarried woman, and a married woman and the comparative probabilities of a diabetic man, an unmarried woman, or a married woman attending a clinic. We must conclude that the data of Munro, Eaton, and Glen are not satisfactory for obtaining an answer to the problem.

Age- and sex-specific death rates for diabetes have been quoted to indicate that there is a greater incidence of diabetes among older women than among older men. The death rates for white males and females are essentially the same to age fifty. Thereafter the death rate for females is greater than that for males, reaching a maximum ratio of about 1.8:1 for the age group of sixty to sixty-nine years.[15] However, unpublished data collected by Lombard[16] show that in Massachusetts among 1,000 adults who died during the period 1949 to 1952 and were known to have had diabetes, only 41.4 per cent of the women and 30.7 per cent of the men had diabetes listed as the primary cause of death. Twenty-five per cent of the death certificates for men and 17 per cent of those for women failed to list diabetes at all. The total number of deaths of men and women with diabetes has been made equal by equating each to 100 per cent. In other words, in this sample the ratio of the number of females who died with diabetes, but not necessarily because of it, to the number of males who died with diabetes, but not necessarily because of it, is 1.0. According to the death certificates which list diabetes as the primary cause of death this ratio is 1.3.

Dahlberg and his co-workers[17] found essentially the same phenomenon in their data. Table 1 (based on their tables 15 and 16) indicates that the proportion of males (based on rates per 1,000) is greater among the living diabetics than among those who died. Their data show also that the proportion of males among those dying of diabetes has been decreasing over the course of time. Joslin and his associates[18] have reported the same thing for the United States, and Harris[19] has reported a similar phenomenon for England. We are left in some doubt, therefore, as to what is the true sex ratio. Here again there is evidence that oft-quoted data may not be pertinent to our problem.

The data required to provide a decisive answer to the question of whether pregnancy plays a statistically significant role in provoking the onset of diabetes are the age- and sex-specific incidence rates of diabetes, with the rates for childless women and women with children given separately. Such data are not available. They could

TABLE 1

Proportion of men among diabetics*

Age	Among living	Among deaths
yrs.	per cent	per cent
30-34	56	50
35-39	70	62
40-44	63	59
45-49	58	55
50-54	61	49
55-59	57	52
60-64	48	} 44
65-69	48	}

*Based on tables 15 and 16, Dahlberg and associates.[17]

be obtained during a survey of diabetes in an entire community such as that done by Wilkerson and Krall.[20]

The closest approach to data of this type of which I am aware are those of Dahlberg, and his co-workers.[17] These investigators made a strenuous effort to detect all *diagnosed diabetics* in the city of Stockholm. They used the State Foods Commission Register of diabetics and the records of all hospitals in Stockholm. On the basis of these data, they were able to compute age- and sex-specific prevalence rates (see table 2). It is interesting to note that the total prevalence rate is slightly greater among men than among women and that the prevalence rate among women exceeds that among men only in the age interval sixty through sixty-nine years. These data suggest, but do not prove, that pregnancy is not of statistical importance as a precipitant of diabetes.

About 60 per cent of the Stockholm diabetics uncovered by Dahlberg and his associates reported their ages at the onset of diabetes. The authors used these data to estimate the age- and sex-specific incidence of diabetes. Unfortunately, the authors do not tell us what population base they employed for these calculations. More importantly, they do not state what proportion of those at each age group supplied data concerning their ages at the onset of diabetes. With statements from only 60 per cent of the sample, it is readily seen that important biases could result. The data are presented in table 3. The incidence is greater among women only in the age intervals 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 75 to 79.

TABLE 2

Age- and sex-specific prevalence rates of diabetes in Stockholm*

Age	Number of diabetics		Diabetics per thousand population	
	Male	Female	Male	Female
0- 4	4	3	0.2	0.2
5- 9	9	13	0.7	1.1
10-14	29	14	2.5	1.2
15-19	46	33	2.6	1.7
20-24	48	45	2.1	1.5
25-29	53	47	1.9	1.4
30-34	66	66	2.4	1.9
35-39	68	38	2.8	1.2
40-44	86	62	4.0	2.3
45-49	84	75	4.2	3.0
50-54	148	115	8.3	5.2
55-59	212	195	13.9	10.5
60-64	197	283	17.2	18.8
65-69	141	226	19.1	20.6
70-74	80	145	18.1	18.2
75-79	49	92	18.2	16.1
80-84	16	32	13.4	11.1
85-	2	2	5.1	1.9
Totals	1,338	1,486	5.1	4.6

*Based on table 3, Dahlberg and associates.[17]

TABLE 3

Age- and sex-specific incidence rates of diabetes in Stockholm*

Age at onset	Male	Female
0- 4	1.11	0.55
5- 9	1.80	1.71
10-14	2.49	2.18
15-19	1.78	1.14
20-24	1.34	0.66
25-29	1.50	1.31
30-34	2.44	1.17
35-39	2.33	1.41
40-44	3.28	1.84
45-49	5.16	4.13
50-54	6.69	8.08
55-59	7.29	10.46
60-64	6.81	7.79
65-69	3.39	4.93
70-74	4.28	1.96
75-79	1.50	2.98
80-84	1.32	0.51
85-	—	—
Totals	2.98	2.71

*Based on table 6, Dahlberg and associates.[17]

In conclusion, it appears that the data are not available for a decisive examination of the statistical importance of pregnancy in precipitating diabetes, and that the available data suggest that pregnancy is not of major statistical importance in the initiation of frank diabetes. This conclusion is in no way intended to imply that pregnancy may not in many cases lead to frank diabetes in prediabetic women. It means only that there is no evidence that statistical genetic analyses will be significantly biased if they fail to consider childless women as a group to be separated from women who have had children.

DIABETES IN THE OFFSPRING OF PREDIABETIC AND DIABETIC MOTHERS

Hoet's suggestion that the uterine environment supplied the fetus by prediabetic and diabetic women is instrumental in precipitating diabetes in children genetically predisposed to the disease is, in principle, in accord with many investigations concerning the expression of gene-determined characters. A few examples will help to make this clear.

Mice carrying the dominant mutation Fused may be entirely normal or show one or more of the following changes: asymmetrical fusions of vertebrae, fusions of ribs at the proximal ends, absence of ribs, bifurcation of the tail tip, and absence of part or all of the tail. Reed[21] has shown that about 50 per cent of the mice carrying the gene are normal in appearance if the mother carries the gene and the father does not, while only about 20 per cent are normal if the mother does not have the gene and the father does.

Wright[22] reports that in some inbred strains of guinea pigs a certain proportion of the animals have extra toes on the hind feet. In the strain with the highest frequency 42 per cent of the animals had extra toes. Since these were highly inbred strains, the animals within a strain were all essentially genetically identical; therefore, the variation among them could not have been genetically determined. Wright was able to show that a very important factor contributing to this variation was the age of the mother. Young females produced more polydactyls than did mature ones.

MacDowell, Furth, Law, and others have demonstrated that the frequency of spontaneous leukemia is lower in crosses between a mouse strain with a high rate and one with a low rate when the female comes from the low-rate strain than when she comes from the high-rate strain. Law states that in the former case the rate is lower still when the females are older than when they are younger. These experiments revealed also that the life expectancy for the mice that died of leukemia as well as those that escaped leukemia is greater for animals born of older mothers than for those born of younger mothers. The above material is reviewed by Law.[23]

The foregoing illustrations will recall the case of mongolism in human beings in which the age of the mother is also an important factor in the causation of the disease, albeit in an exactly opposite manner to that for the above cases, older mothers being more likely than younger mothers to give birth to a mongol.[24]

The etiology of erythroblastosis fetalis is an excellent example in human beings of the interaction of the fetus' genotype (genetic composition) with the environment provided by the mother. Erythroblastosis fetalis will not develop if the mother does not have a circulating antibody to an antigen present in the fetus' red cells. The red cell antigens are genetically determined. It has been demonstrated repeatedly that it is not the child's genotype as such that leads to the disease, but the combination of the child's genotype plus an appropriate antibody produced by the mother.

The illustrations described thus far were not concerned with known changes in the external environment impinging on the embryo through their effect on the mother. Such effects, however, are well-known. Some illustrations will demonstrate their relation to genetic phenomena. It has been amply demonstrated that various vitamin deficiencies and poisons can affect the development of mammalian young, presumably through their effect on the mother.[25] Recent work has demonstrated that in mammals, as in other vertebrates and invertebrates, the response of the embryo is conditioned by its genotype. As an example, one such experiment in mice involving the effect of cortisone on the occurrence of cleft palate will be described.[26]

Pregnant mice of three different inbred strains were treated with 2.5 mg. of cortisone daily for four successive days. The course of treatment was begun on different days of gestation in different experiments. Table 4 presents a summary of the data obtained when treatment was begun on the tenth day of gestation. In two of the strains (A and N) a very high proportion of the mice derived from treated females had cleft palates; in the third strain (C57) a much lower proportion had cleft palates. These strains were highly inbred and were reared under controlled conditions. The difference in response must be assumed to be due to genetic differences between the "sensitive" strains (A and N) and the "resistant" strain (C57). Crosses between the A strain (sensitive) and the C57 strain (resistant) support this conclusion. Fewer offspring of treated A females had cleft palates when such females were mated to C57 males than when they were mated to A males. It is clear from these experiments that the genetic constitutions of the mother and of the fetus determine the frequency with which cleft palate will occur in the offspring in response to a given

TABLE 4

Incidence of cleft palate among offspring of pregnant mice treated from the 10th through the 13th day of pregnancy with 2.5 mg. of cortisone per day*

Cross	Number of offspring	Cleft palate No.	Cleft palate Per cent
A ♀ x A ♂ or N ♀ x N ♂	30	30	100
C57 ♀ x C57 ♂	78	14	18
A ♀ x C57 ♂	31	16	52
C57 ♀ x A ♂	65	3	5

*Based on table 1, Fraser and associates.[26]

course of cortisone.

These experiments, as well as those reviewed by Warkany,[25] recall the correlation between rubella in the first trimester of pregnancy in human beings and various abnormalities shown by the resulting offspring.[27]

The examples discussed thus far concern changes which are present congenitally. While it is true that most examples reported are of this type, others exist in which the "maternal" effect does not become evident until considerably later in the offspring's life. Most of these examples concern studies of the development of spontaneous cancer, primarily, because only in cancer experiments are animals retained to determine the presence or absence of a maternal effect in older animals. Other experiments are designed to detect congenital deviations only. The data have recently been reviewed by Wooley.[12] (See also the earlier discussion of leukemia.)

Hoet's suggestion that the prediabetic or diabetic condition of a pregnant woman might affect the expression of the disease in her child is, as we have seen, in complete agreement with genetic thinking on such problems. Here, as in the case of the effect of pregnancy on the mother, the question is not "Is this possibility in contradiction to genetic theory?" but rather "Is this phenomenon — if it occurs — sufficiently frequent to affect statistical genetic studies?"

Steinberg and Wilder[28] have already investigated one aspect of this problem with exactly the point of view expressed by Hoet in mind. They were statistically evaluating the phenomenon of "anticipation." After establishing, on the basis of three independent sets of data, that the statistical evidence indicated that prior onset of diabetes occurred in the child of an affected parent only about as frequently as one might expect by chance, these authors stated:

"Among the reasons for the reluctance of some workers to consider the phenomenon of anticipation as being of physiologic significance are the facts that no instance of anticipation has been discovered in animals other than man and that no satisfactory biologic explanation for it has been offered. In the case of diabetes, however, there is a possible biologic rationale for anticipation when the patient's mother is diabetic. This may be based on the recognition that many infants born of prediabetic and diabetic women evidence characteristic abnormalities. It may be assumed that this unfavorable uterine environment causes earlier onset of diabetes among the offspring in whom the disease will subsequently develop. This does not apply when the patient's father is the affected parent because children of diabetic fathers do not suffer from these disabilities."

Steinberg and Wilder then examined the data derived from 124 patients with diabetic mothers and 76 patients with diabetic fathers. They concluded that "the unfavorable uterine environment provided the fetus by diabetic or prediabetic mothers is not a *major* factor in determining the age of onset of diabetes in their diabetic offspring."

Examination of the data from a larger sample (which included the above cases) of 186 patients with affected mothers and 115 patients with affected fathers revealed that the frequency of prior onset was 63.4 per cent for the former group and 63.5 per cent for the latter (based on data used by Steinberg and Wilder in their study of the genetics of diabetes). Analyses of these data similar to those reported by Steinberg and Wilder[28] entirely confirm their earlier conclusions.

Finally, if the prediabetic or the diabetic state in the mother tended to precipitate diabetes in their susceptible offspring in an appreciable number of cases, the frequency of affected offspring should be greater in families with a diabetic mother than in families with a diabetic father. Table 5 (based on data from Steinberg and Wilder[4] indicates that the frequency of diabetic offspring is the same regardless of which parent is affected.

TABLE 5

Frequency of diabetes among the sibs of diabetic patients with one diabetic parent*

Diabetic parent	Number of patients	Sibs		
		Total	Diabetic	
			No.	Per cent
Mother	220	1,000	113	11.3
Father	150	620	72	11.6
Total	370	1,620	185	11.4

*Based on data from Steinberg and Wilder.[4]

We may conclude that the available evidence does not indicate a major effect of maternal diabetes on the frequency of diabetes in the child.

SUMMARY

1. The data necessary for a decisive evaluation of the statistical importance of pregnancy as a precipitant of diabetes are not available.

2. The data that are available suggest that pregnancy is not of statistical importance in the initiation of frank diabetes.

3. The prediabetic state in the mother is not of statistical importance in determining the age at onset of diabetes in her diabetic children.

4. The prediabetic state, as such, in the mother is not a statistically significant influence in determining whether or not her child will become diabetic.

5. This analysis has no bearing on the specific clinical problems discussed by Hoet so far as they refer to individual patients.

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SUMMARIO IN INTERLINGUA

Hereditate e Anticipation in Diabete Mellite in Relation al Metabolismo de Hydratos de Carbon Durante le Pregnantia

1. Le datos que esserea necessari pro un evalutation decisive del importantia statistic del pregnantia como precipitante de diabete non es disponibile.

2. Le datos que de facto es disponibile suggere que pregnantia non es de importantia statistic in le initiation de franc diabete.

3. Le stato prediabetic del matre non es de importantia statistic in determinar a qual etate/diabete se declara in su prole diabetic.

4. Le stato prediabetic del matre non es, in se mesme, de influentia statisticamente significative in determinar si o non le prole va devenir diabetic.

5. Iste analyse non affice le specific problemas clinic discutite per Hoet in tanto que illos concerne patientes individual.

Acquired Insulin Resistance

A Case Report

Michael Kaye, M.B., B.S., Eleanor McGarry, M.D.,†*
and Isidore Rosenfeld, M.D.,‡ Montreal

Insulin resistance, usually defined as a condition in which a diabetic requires a dosage of insulin in excess of 200 units daily, is uncommon. Most of the reported cases have been associated with diabetic keto-acidosis, allergy to insulin, or a variety of other diseases. The following case is reported because none of these conditions was present and the opportunity for detailed investigation was possible. This disclosed, among other things, the presence of an insulin-neutralizing factor in the patient's serum.

CASE HISTORY

E. R., No. 53-552, a 36-year-old married woman, was first diagnosed as having diabetes mellitus in 1943; at this time she was 5 feet in height and weighed 70 kg. Admission to another hospital at that time revealed nocturia, glycosuria without ketonuria, and a fasting blood sugar of 312 mg. per 100 cc. Her diabetes was readily controlled with crystalline insulin, and she was discharged on diet alone. Subsequently, although her diabetic control was poor, she took insulin only intermittently.

The patient was admitted to this hospital Jan. 9, 1953, complaining of lower abdominal pain, frequency of urination with dysuria, and thirst. No insulin had been taken since the summer of 1952. There was no history of allergy. Examination revealed moderate dehydration. The temperature was 99.3, the pulse 135, and the respirations, 36. The blood pressure was 125/90. There was tenderness in both costovertebral angles; the remainder of the physical examination was normal. Urinalysis and culture confirmed the presence of a urinary tract infection, which was rapidly controlled with penicillin and sulfisoxasole. Subsequent to the first three days in hospital the patient felt well, was afebrile, and had no symptoms except those described below in direct connection with her diabetes.

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COURSE OF DIABETES IN HOSPITAL

On admission, the urine contained 6.2 per cent reducing sugar and gave a positive reaction for ketones. By the next day, no ketones could be detected, and thereafter at no time was ketonuria or ketonemia present. The initial finding was probably the result of decreased food intake associated with the acute infection. The dosage of crystalline insulin* was progressively increased until on February 6, the patient was receiving 1100 units per day in five divided doses. On this date for the first time her urine became sugar free. Insulin reactions over the next two days necessitated reduction in insulin dosage to between 500 and 700 units per day, and on this amount her control was good. This is shown graphically in figure 1.

Attempts to modify the insulin resistance by intravenous administration of insulin, the use of pork insulin, or insulin which had been denatured by heat were unsuccessful. The diet, which since admission consisted of 80 gm. of protein, 50 gm. of fat, and 150 gm. of carbohydrate, giving 1400 calories, was increased on February 25, to 80 gm. of protein, 90 gm. of fat, and 172 gm. of carbohydrate, giving 1870 calories. This diet remained constant thereafter. Twenty-four hour urine specimens had been examined for sugar from admission, but a more complete study was instituted on January 28, which is called day 1. This was expanded to include nitrogen and electrolyte balances on day 29, figure 2.

On February 20, day 23 of the study, the insulin was discontinued. Thereafter until day 43 none was given except for sensitivity tests. There was a rise in the fasting blood sugar, which ranged between 305 and 424 mg. per 100 cc. The urinary sugar was about 100 gm. per day, with a peak of 167 gm. In spite of this, the patient felt well and denied thirst or polyuria. As already stated,

*All insulin used, unless otherwise stated, was beef crystalline zinc insulin prepared by Connaught Laboratories, Toronto.

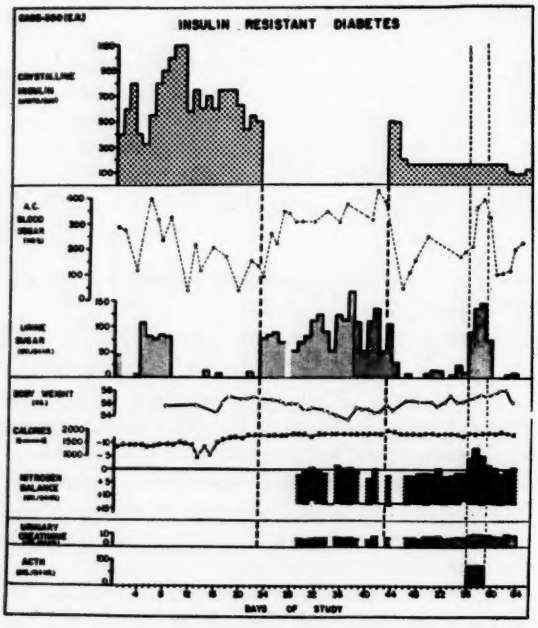

FIG. 1. The effect of insulin on blood and urine sugar.

there was no ketonuria or ketonemia. A gradual decline in weight occurred, from 56.8 to 54.7 kg.

On March 12, day 43, insulin was started again with 500 units per day in divided doses. The following day, the patient received 480 units, and the next morning she developed a severe insulin reaction. The insulin dosage was progressively reduced until on 160 units per day in four doses glycosuria was minimal and blood sugar values were within the normal range.

A course of corticotropin (Acton X), 20 units twice daily, was given from day 56 to day 59, inclusive. Although insulin and diet were unchanged, marked glucosuria up to 145 gm. per day and hyperglycemia as high as 390 mg. per 100 cc. fasting developed. After cessation of corticotropin, there was a temporary rebound effect, with insulin reactions on days 62 and 63. It is interesting that the patient complained of thirst for the first time while on corticotropin. She was discharged on April 4, day 66, on the same insulin dosage as before the course of corticotropin.

SUBSEQUENT COURSE

The patient's status remained unchanged until June 1953, when she had to be readmitted for a recurrence of the urinary infection. This again responded quickly to therapy. Diabetes was well controlled on four doses

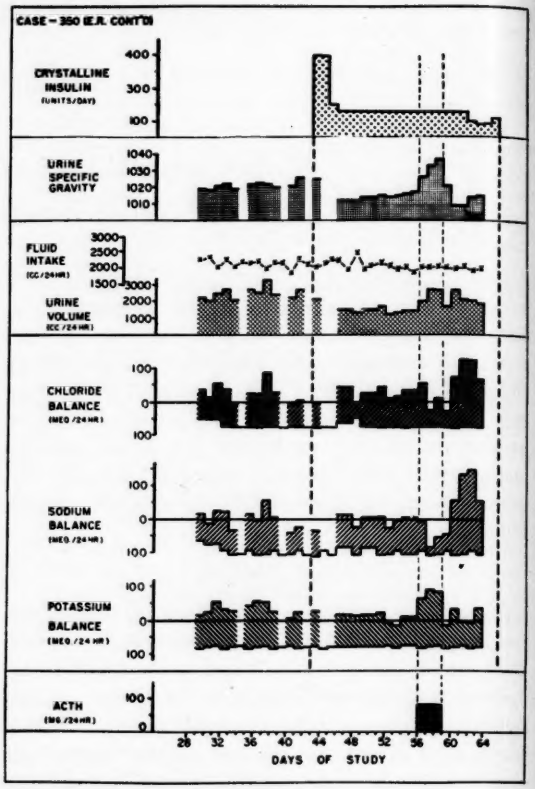

FIG. 2. Electrolyte and nitrogen balances.

of 40 units of crystalline insulin. She was discharged after two weeks in the hospital on 80 units of protamine zinc insulin and 32 units of crystalline insulin before breakfast and 32 units of crystalline insulin before lunch, with satisfactory control.

LABORATORY FINDINGS

The urine on admission contained protein graded ++ and pus in clumps. Thereafter no protein was detected and only 3 to 5 pus cells were present in a centrifuged specimen. Urine culture grew micrococci. Urea clearance was 102 per cent of normal, and ammonia, titratable acidity, and *p*H were all within normal limits.

The hemoglobin was 95 per cent and the red cell count 4,900,000. The white cell count was 7,000, with a normal differential. Eosinophils were never above 1 per cent. The sedimentation rate varied between 43 and 29 mm. in one hour. The Wassermann and Kahn reactions were negative.

Biochemical studies were as follows: nonprotein nitro-

gen 22.1 mg. per 100 cc.; serum proteins 7.08 gm.; albumin 4.58 gm., and globulin 2.5 gm. per 100 cc. Thymol turbidity was 12.1 units, and thymol flocculation was negative; the cephalin cholesterol flocculation was negative and the bromsulfalein test showed 6.8 per cent retention in thirty minutes. The serum total lipids were 700 mg. per 100 cc., fatty acids 389 mg.; phospholipids 8.8 mg.; cholesterol 209 mg.; and cholesterol esters 129 mg. These determinations were repeated at biweekly intervals, together with the serum electrolytes, calcium, and phosphorus, both when off and on insulin. All failed to show any change and except for the slightly elevated thymol turbidity were within the normal range.

Apart from the expected changes occurring with the administration of corticotropin, the electrolyte and nitrogen balances revealed nothing of note. These are shown in figure 2.

The glutathione content of ten samples of blood drawn fasting between day 25 and day 36 varied between 2.8 and 4.0 mg. (normal 3.8 mg. ± 0.7), expressed as sulfhydril groups in milligrams per 100 cc. corrected for 50 per cent hematocrit. There was no correlation between the glutathione level and the clinical course.

A galactose tolerance test was done on day 16. The patient was fasted after 8 p.m. the previous evening. The insulin requirements were 750 units at this time and the usual 4 a.m. dose of 150 units was reduced to 100 units. The results are shown in table 1. A very small rise in blood galactose is noted, indicating rapid conversion to glucose.

TABLE 1
Galactose tolerance test

Time	Blood glucose (mg. per 100 cc.)	Blood galactose (mg. per 100 cc.)
8:00 a.m.	204	
8:30 a.m.	197	
9:00 a.m.	194	
Galactose, 40 gm. orally		
9:30 a.m.	228	0
10:00 a.m.	237	2.5
10:30 a.m.	242	4.2
11:00 a.m.	212	0

Insulin sensitivity tests were performed fasting, no insulin having been given since midnight the evening before. Forty units of crystalline insulin were injected intravenously on each occasion. The results are shown in table 2.

TABLE 2
Insulin sensitivity tests

Day	0	15 min.	30 min.	60 min.	Per cent fall
22	154	128	117	117	24
37	373	339	335	309	17
50	248	216	192	159	36
58*	362	392	344	326	10
60	321	296	296	262	18

*Insulin had been boiled for 30 minutes; 48 units were used.

Tests for insulin-neutralizing activity in the patient's serum drawn on March 9, 1953, day 41, were performed using the technic described by Lowell.[1] The first series was done in March. The serum was then stored at —10° C. and a further series of tests were done in January 1954. There was no difference in the neutralizing activity of the patient's serum before and after storage.

Adult male mice fasted for sixteen hours, but with free access to water, were used. Blood sugar determinations were made by the Folin-Wu method on 0.1-ml. samples from the tail veins, using 0.26 mg. of heparin as anticoagulant. After some practice blood was obtained without difficulty. After taking the first blood sample, 0.2 ml. of the patient's serum plus 0.01 unit of crystalline insulin mixed just prior to injection were given intraperitoneally in a total volume of 0.7 ml. The serum of a diabetic responsive to insulin in usual doses was employed as a control. Both sera were dialyzed before use to make them almost sugar-free. Subsequent blood samples were then obtained at thirty and sixty minutes. As these were usually the same, a single forty-five minute specimen was later obtained. The results are shown in table 3.

TABLE 3
Tests done in March 1953 to demonstrate insulin-neutralizing activity of the patient's serum

Group	No. of animals	Average per cent change in blood sugar	Standard deviation
Patient's serum and insulin	5	+ 3.1	7.44
Control serum and insulin	6	—52.6	14.73
Patient's serum and saline	6	— 7.8	26.3
Control serum and saline	5	— 7.1	15.1

It is apparent that the patient's serum completely prevented the fall in blood sugar, which was seen when the control serum was used.

Using a method of starch electrophoresis, to be described in detail in a separate publication,[2] the patient's serum was separated into six fractions, albumin, alpha, beta, gamma 1 and 2 globulins, and the starch blank adjoining the gamma 2 globulin fraction. Each fraction was then assayed in the mice, using the same quantitative amount of material as present in the original serum. The results are shown in table 4.

TABLE 4

Tests done in January 1954 to show with which protein fraction the insulin-neutralizing factor is associated

Group	No. of animals	Average per cent fall in blood sugar	Standard deviation	P values 0	T^2	T^1
0 (starch blank)	14	22.6	16.15			
T^2	12	5.5	15.75	<0.05		<0.01
T^1	8	27.5	13.27		<0.01	
B	8	49.8	9.83			<0.01
A	7	44.6	7.62			<0.01
Albumin	6	42.4	15.23	<0.05	<0.01	<0.1
Patient's whole serum	7	6.4	10.39			
Control serum	4	48.6	6.42			

Maximum neutralizing activity is in the gamma 2 globulin fraction, with smaller amounts in the starch blank and gamma 1 globulin. These probably represent incomplete separation of the active principle.

Electrophoresis of the patient's serum in the Tiselius apparatus after storage for ten months showed it to contain albumin 51.22 per cent, alpha[1] globulin 3.61 per cent, alpha[2] 10.28 per cent, beta 15 per cent, and gamma 19.89 per cent. The beta and gamma globulins were elevated above normal.

Endocrine assays included gonadotropins (F.S.H.), positive at 13.2 mouse units per twenty-four hours and negative at 52.8 mouse units per twenty-four hours. The biologic corticoids were 46 glycogenic units per twenty-four hours and the 17 keto-steroids 4.2 mg. per twenty-four hours. The basal metabolic rate was —4 per cent. All these are within normal limits.

Allergy tests included skin testing to crystalline, protamine, and globin insulin. No difference from controls done at the same time was seen. The Prausnitz-Kustner test, using crystalline insulin, was negative. The precipitin test, using crystalline insulin, 80 units per cubic centimeter as antigen, was negative on two occasions, both at times of maximal insulin resistance.

Radiologic examination of the skull, chest, and urinary tract by excretory and retrograde pyelography was normal.

DISCUSSION

Comprehensive reviews of the literature dealing with insulin resistance have been published.[3-5] Associated conditions have included disorders of the hepatobiliary system, pancreatic disease, endocrine diseases, infections of different types, keto-acidosis, and insulin allergy, either localized or generalized. No clinical or laboratory evidence of any of these conditions was present in this patient.

Insulin, although a protein, is a very weak antigen. In some cases circulating antibody has been demonstrated by the precipitin test,[6] by insulin-neutralizing effect, and recently by using a hemagglutination technic.[7] In patients with allergic manifestations, antibody may sometimes be shown by the passive transfer test.[6] Intermittent administration of a foreign protein is an excellent way to stimulate antibody production and has been suggested as important in insulin resistance.[6] In this patient, insulin was injected at intervals over several years and may have been a factor in the development of her resistant state.

Localization of the insulin-neutralizing factor predominantly in the gamma[2] globulin fraction is compatible with the previously expressed views that it is an antibody to insulin,[8] and confirms the findings of Filippis and Iannacone.[9] The presence of cutaneous reactions or systemic anaphylactic phenomena to insulin probably depends on a separate antibody,[8] there being no necessity for both to be present at the same time, in the same protein fraction,[10] or, indeed, in the same patient.

There was no evidence that the results obtained in the mice experiments were due to a hyperglycemic principle in the patient's serum, since injection of the serum alone into mice did not produce hyperglycemia.

In view of the known action of corticotropin and adrenocortical hormones to affect some immunologic mechanisms,[11] and because of reported benefit from corticotropin administration in a case of insulin resistance,[12] it was believed that its use in this patient would be of interest. Although her insulin requirement at this time was only 160 units per day, this is considerably more than the dose known to have controlled her dia-

betes several years previously. Marked aggravation of the diabetic state occurred with corticotropin, and for this reason it was discontinued. The temporary period of increased sensitivity after cessation of the hormone may have been due to transitory depression of endogenous corticotropin with temporary adrenal insufficiency.

The ability of this patient to withstand inadequate carbohydrate utilization over a prolonged period of time without developing any apparent abnormality in fat metabolism is interesting. The distinction between the young labile diabetic who rapidly develops ketosis on insulin withdrawal and the obese elderly person in whom ketosis is uncommon comes to mind. This patient would apparently fall into the latter group, in spite of the marked hyperglycemia and glycosuria.

Maintenance of good diabetic control in patients with insulin resistance is difficult but probably worth-while, even though it necessitates the daily injection of large amounts of insulin. Often after a period of weeks or months the resistance will decrease. Although denaturing the insulin protein by heat may be of value in cases with allergic symptoms,[13] in this patient it did not seem to be of any value. If an approximate idea of the daily insulin requirement can be obtained, the administration of the full requirement after several days during which no insulin has been given may alter the degree of resistance. This seemed to occur in this patient when insulin was reinstituted on day 43. In this regard the insulin sensitivity tests, using 40 units of crystalline insulin intravenously, were a good guide to the degree of resistance present at any one time in this patient.

SUMMARY

A case of idiopathic insulin resistance in a diabetic is described. The patient's serum contained a factor in the gamma globulin fraction capable of neutralizing the hypoglycemic action of insulin.

ACKNOWLEDGMENTS

We wish to thank Dr. W. de M. Scriver and Dr. J. Brabander for permission to report this case and Miss Eleanor Davidson for technical assistance.

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SUMMARIO IN INTERLINGUA

Acquerite Resistentia a Insulina: Reporto de un Caso

Es describite un caso de idiopathic resistentia a insulina in un patiente diabetic. Le sero del patiente contineva in le fraction de globulina gamma un factor capace a neutralisar le effecto hypoglycemic de insulina.

Diabetic Coma and Pituitary Necrosis in an Acromegalic Patient

A Case Report

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Pituitary destruction or hypofunction occurring in the course of diabetes mellitus is usually followed by insulin sensitivity, hypoglycemia, and amelioration of the diabetes. The patient whose case is recorded herein suffered from acromegaly, presented with diabetic coma, and died in pituitary apoplexy following necrosis of an eosinophilic tumor without apparent reduction in severity of the diabetic state.

CASE HISTORY

A forty-nine-year-old man was admitted in diabetic coma, glycosuria having been discovered first a few hours previously. He had suffered from thirst, polyuria, loss of weight, and cramps in the legs for nearly two months but had been able to work and had not sought medical advice. These symptoms establish an antecedent diabetes beyond reasonable doubt.

The year before, the patient's physician had diagnosed myxedema because of coarsening of the facial features, and he had taken 3 gr. of thyroid a day ever since. There was no known history of headaches, visual disturbances, or enlargement of the hands or feet. Thirty-six hours before admission the patient felt unwell, and after returning from work he became mentally confused. That night his breathing was noticed to be heavy, but next morning he felt better and ate breakfast. Later in the day he vomited, and after becoming drowsy and more irrational he passed into coma four hours before reaching the hospital.

PHYSICAL EXAMINATION

The patient was a heavily built man with a prominent lower jaw, heavy orbital ridges, and large hands characteristic of moderately advanced acromegaly. He was dehydrated, had air hunger and smelt of acetone, and resisted examination in spite of being comatose. His condition was not typical of diabetic coma, restlessness and episodes of violence suggesting a complicating cerebral factor. The pulse was 128 and the blood pressure 120/70. There were no signs of disease in the heart, lungs, or abdomen. Examination of the central nervous system was difficult and failed to reveal any localizing signs, yet the pupils were unequal in size and moderately dilated and failed to react to light. Signs of papilledema and retinopathy were absent.

LABORATORY DATA

At admission, the urine contained sugar graded four plus. The Rothera test was three plus, the ferric chloride one plus. The test for albumin was two plus and chlorides zero. The blood sugar was 740 mg. (Folin and Wu). After six hours of treatment the serum sodium was 320 mg. per 100 ml. (139 mEq.), the serum potassium 13.7 mg. per 100 ml. (3.5 mEq.), the plasma chlorides 369 mg. per 100 ml. (104 mEq.), the alkali reserve 34 vols. carbon dioxide, and the blood urea 56 mg. per 100 ml.

TREATMENT AND PROGRESS

In the first eight hours the patient was given 140 units of soluble insulin subcutaneously and a total of 4.5 liters of normal and later 0.18 per cent saline intravenously. There was definite clinical improvement by this time, and he would respond slowly to loud speech. The blood sugar had fallen to 280 mg. per 100 ml.

Four hours later in spite of a blood pressure of 140/90 and a blood sugar of 210 mg. he became more deeply comatose. He had pinpoint pupils, Cheyne-Stokes respiration, and equivocal extensor plantar reflexes. He was occasionally violent and had to be given paraldehyde intramuscularly and barbiturates parenterally. In case that acute liver failure should be an added cause of coma he was also given 20 gm. of glutamic acid intravenously and large doses of vitamin B complex; this treatment was without benefit.

Twenty hours after admission the temperature was 103.4° F. Aureomycin was given in addition to the usual prophylactic penicillin and streptomycin. The patient's diabetic condition gave rise to no anxiety, since the blood sugar averaged 230 mg. with 10 to 20 units of insulin every four hours, while an infusion of 4 per cent glucose

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in 0.18 per cent saline was continued; the serum potassium remained in the region of 14 mg. per 100 ml.

During the last twenty-four hours the patient remained deeply comatose and cyanosed, with shallow and irregular respiration. The temperature rose to 104.6° F. and he died suddenly without signs of peripheral circulatory failure.

POST-MORTEM EXAMINATION

Thirty-six hours after death the body was 188 cm. in height with definite signs of acromegaly. The heart weighed 375 gm. (normal 355 ± 40 gm.) and was normal save for a small auricular septal defect, with healthy coronary arteries. Examination of the skull and brain revealed no sign of subarachnoid or intracerebral hemorrhage, and the vessels were normal. The pituitary gland was almost entirely necrotic and consisted of brown semi-liquid material with a slight rim of glandular tissue. Slight enlargement of the sella turcica with bulging of the diaphragma sellae suggested a tumor, although the growth had not extended beyond the fossa.

The anterior pituitary tissue which remained was composed of eosinophilic tumor cells arising from an adenoma which had undergone widespread necrosis and liquefaction. There was no microscopic evidence of significant recent hemorrhage.

DISCUSSION

The importance of the anterior pituitary in carbohydrate metabolism has been shown by the work of Houssay[1] and Young,[2] and the association of acromegaly and diabetes is well recognized.

In reviewing 650 cases of acromegaly in which the results of urine analysis were available, Atkinson[3] found glycosuria in 32 per cent, and 18 patients were considered to have died in diabetic coma, mostly before insulin was available. Coggeshall and Root[4] also found glycosuria in 36 per cent of the 153 cases which they reviewed, but only 9 patients with acromegaly were seen in a series of 30,000 diabetics, indicating that this disease is an infrequent factor in the etiology of diabetes. On the other hand, hypopituitarism leads to spontaneous hypoglycemia, as emphasized by Sheehan and Summers,[5] and increased insulin sensitivity has been noted should this develop in diabetic patients (Lyall and Innes,[6] Kotte and Vonderahe,[7] Feldman and his associates,[8] Clark, Franklin and Sahs,[9] Williams,[10] Poulsen,[11] Root,[12] and Martin and Pond[13]).

Complete pituitary necrosis usually takes two or three days to develop, and there may be insufficient time for endocrine dysfunction to become apparent before death.

A characteristic clinical syndrome resulting from acute pituitary necrosis has been described by Brougham, Heusner and Adams[14] as pituitary apoplexy. They observed five patients in whom evidence of pituitary adenomas had been present for some years before sudden necrosis of the tumor led to pituitary apoplexy, which was fatal in all but one case. Common signs and symptoms included sudden headache, diplopia, amblyopia, drowsiness, confusion, and eventually coma. Fever, unequal or fixed contracted pupils, and neck rigidity were also encountered, and death usually occurred after a few days. One of their patients was a woman with diabetes who did not apparently show signs of hypoglycemia before death. Factors responsible for the necrosis included the tumors outgrowing its blood supply, compression of blood vessels by growth extending beyond the pituitary fossa, and primary thrombotic occlusion. Changes were seen in the cerebrospinal fluid such as the presence of red and white cells, xanthochromia, increase in protein, and elevation of the pressure.

The frequency of fever may be explained by irritation of the anterior hypothalamus due to pressure from the tumor or a bulging pituitary diaphragm, or because of a local meningitis. The differential diagnosis may be difficult. In my case, the typical diabetic history, followed by loss of consciousness, hyperglycemia, and ketosis, suggested diabetic coma as the prime cause, and the initial response to insulin and fluids given intravenously supported such a diagnosis. Later, the increasing depth of coma, restlessness, pinpoint pupils, irregularity of respiration, and pyrexia suggested either a cerebral cause such as a tumor, meningitis or subarachnoid hemorrhage, or acute liver failure. The paradox of pituitary destruction in the presence of severe diabetic ketosis was never considered, and the correct diagnosis was revealed only at autopsy.

The diagnosis of pituitary apoplexy should be considered in a comatose patient with a history of a pituitary tumor, even in the presence of severe diabetes. When destruction of the anterior pituitary is rapid and death takes place in a few days, no amelioration of the diabetes can be expected.

SUMMARY

A forty-nine-year-old man became comatose after a brief period of drowsiness and confusion and was found to have acromegaly and diabetic ketosis. In spite of a satisfactory initial response to insulin he died with signs of pituitary apoplexy. At autopsy a necrotic eosinophilic pituitary tumor was discovered.

ACKNOWLEDGMENTS

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SUMMARIO IN INTERLINGUA

Coma Diabetic e Necrosis Pituitari in un Patiente Acromegalic. Reporto de un Caso

Es reportate le caso de un homine de 49 annos de etate qui deveniva comatose post un breve periodo de somnolentia e confusion e in qui esseva constatate acromegalia e ketosis diabetic. In despecto de un satisfacente responsa initial a insulina, ille moriva con signos de apoplexia pituitari. Al autopsia esseva discoperite un tumor pituitari eosinophilic necrotic.

ABSTRACTS

Alvarez, Luis M.; Pupi, Roberto; Raffaele, José (*Dept. of Nutrition Hosp. Rivadavia, Buenos Aires, Argentina*): INSULIN-RESISTANCE. Prensa méd. argent. *41*:2736-40, Sept. 17, 1954.

Insulin-resistant diabetes is described as a situation in which the insulin requirement is 200 units daily for more than 48 hours without acidosis or coma being present. Two cases of insulin resistance are described with insulin requirement of 600 units and 450 units as a mixture 2:1 respectively. (Spanish)

Antes, Earl H. (*420 Cherry St., Evansville, Ind.*): CHARCOT JOINT IN DIABETES MELLITUS. J.A.M.A. *156*:602-03, Oct. 9, 1954.

All patients with diabetic neuropathy should have the feet studied routinely by X ray. Rapid destruction of the tarsals, metatarsals, and proximal phalanges occurred in a patient with long-standing, poorly controlled diabetes. No significant infection or vascular changes were seen, even though there were marked sensory disturbances and marked objective evidences of neuropathy, including absent reflexes. Definite improvement was noted after diabetic control and immobilization procedures were carried out.

Armstrong, C. N.; Lloyd, W. H. (*Royal Victoria Infirmary, Newcastle-upon-Tyne, England*): SEVERE LOCAL AND GENERAL REACTION TO INSULIN ZINC SUSPENSION AND SOLUBLE INSULIN. Brit. M. J. *2*:396-97, Aug. 14, 1954.

The authors present the case of a 47-year-old man with diabetes who after 11 days of receiving insulin zinc suspension developed large bullae at the sites of injection and generalized malaise with anorexia and nausea. Spontaneous desensitization occurred within 3 weeks.

Azerad, E.; and Lestradet, H.: STUDIES ON DIABETIC KETOSIS AND "ACIDOKETOSIS": DEFINITION AND LIMITS OF DIABETIC COMA: ELEMENTS OF A TERMINOLOGY. La semaine des hôpitaux de Paris *28*:3139, Oct. 22, 1952. (Abstr. from J.A.M.A. *151*:526, Feb. 7, 1953.)

Ketosis depends on the ketone bodies retained in the body rather than on those excreted in the urine; therefore, measurement of ketonemia is important. Acidosis and ketosis differ in their manifestations and effects and should not be confused; ketonemia alone does not show acidosis. There was an almost perfect correspondence between the blood *p*H and the state of consciousness in these patients. The *p*H drops when precoma begins, and the resulting acidosis is apparently one of the factors, if not the main factor, governing loss of consciousness. Cure should not be considered established until consciousness has not only been restored but the *p*H has also been brought back to about 7.4 and the ketone bodies have disappeared completely from the blood.

Bile, Giovanni (*Rome, Italy*): OSTEOARTICULAR SYNDROME IN DIABETES. La Diagnosi *10*:333-43, August 1954.

Osseous and osteoarticular alterations are frequently seen in diabetes. The spine is the most frequent place for these abnormalities, such as osteoporosis and hypertrophic arthritis. A hormonal imbalance in the course of diabetes can be held responsible for their occurrence, particularly following climacteric changes. (Italian)

Bogdanove, E. M.; and Lipner, H. J. (*Dept. of Anatomy, State Univ. of Iowa, Iowa City, Iowa*): INTESTINAL ABSORPTION OF GLUCOSE IN HYPOTHALAMIC OBESITY. Proc. Soc. Exper. Biol. & Med. *81*:410-12, November 1952.

Hypothalamic obesity was produced in rats by means of electrolytic lesions. Determinations of intestinal absorption of glucose yielded the following coefficients of glucose absorption: in normal control animals, 114.0; in rats with hypothalamic lesions, 107.4; in such rats given thyroxin, 173.5; in control rats given thyroxin, 191.6; in control rats subjected to thyroidectomy, 75.2. These results indicate that the intestinal absorption of glucose need not differ from control values in order for obesity to occur. Thyroxine elevated the coefficient of glucose absorption in rats with hypothalamic lesions as well as in control animals without such lesions. Rats without these lesions thyroidectomized and treated with thyroxin served as method controls. Observations of rats with

hypothalamic lesions which did not exhibit excessive weight gain suggest that these lesions may interfere with the secretion of growth hormone by the pituitary.

Bohan, Edward M. (*Dept. of Metabolism, St. Francis Hosp., Wilmington, Del.*): DIABETES MELLITUS IN JUVENILE IDENTICAL TWINS. Delaware M. J. *26*:285-92, November 1954.

Diabetes mellitus often occurs simultaneously in identical twins but environmental factors and cytoplasmic asymmetry may upset the law of heredity. Sometimes the age of onset of diabetes may be different and sometimes only one twin may develop the disease.

Boulin, R.; Meyer, F. W.; Gueniot, M.; and Lapresle, C.: TREATMENT OF DIABETIC COMA WITH INSULIN AND COCARBOXYLASE. La semaine des hôpitaux de Paris, *28*:2069, July 2, 1952 (Abstr. from J.A.M.A. *150*:1353, Nov. 29, 1952).

The authors claim excellent results obtained in cases of diabetic coma treated with a combination of insulin and cocarboxylase. They believe that the amount of insulin needed for recovery is substantially reduced when it is combined with cocarboxylase. Four injections of cocarboxylase are given in average cases, and six in severe ones. Prolonged use of massive doses of cocarboxylase may result in hypoglycemia.

Burch, G. E. (*Dept. of Med., Tulane Univ. Sch. of Med. and Charity Hosp. of Louisiana, New Orleans, La.*): THE ELECTROCARDIOGRAM AND DISTURBANCES IN ELECTROLYTE BALANCE. A.M.A. Arch. Int. Med. *94*:509-12, October 1954.

The electrocardiogram more frequently and more reliably indicates the existence, rather than the type and degree, of electrolytic disturbance. Serious difficulties and errors in judgment are not likely to arise if the electrocardiogram is not used as an infallible standard, and if its limitations are recognized.

Caroli, J.; Eteve, J.; and Bertrand, J.: DIABETES MELLITUS CURED BY LAENNEC'S CIRRHOSIS. La semaine des hôpitaux de Paris *29*:607-26, Feb. 15, 1953 (Abstr. from J.A.M.A. *152*:653, June 13, 1953).

Improvement in diabetes mellitus may occur in the course of cirrhosis. It is not explained by incidental restrictions in carbohydrate intake since it may persist despite a high caloric diet rich in carbohydrate. The antidiabetic effect of destruction or removal of liver tissue is further shown by the fact that: (1) removal of the liver in animals at the time of pancreatectomy prevents completely the hyperglycemia that would normally occur after removal of the pancreas, and (2) removal of the liver subsequent to pancreatectomy causes a sharp drop in the elevated blood sugar. Hyperglycemia and glycosuria can be artificially produced by cortisone, but these effects do not develop after hepatectomy.

In a case of diabetes mellitus with cirrhosis, necropsy revealed that the improvement in the patient's diabetes mellitus was not due to a pronounced decrease in the amount of functional hepatic parenchyma, since the lobular parenchyma was fairly well preserved despite annular cirrhosis. Pronounced hyperplasia of the islands of Langerhans involving mainly the beta cells and a small chromophobe adenoma of the pituitary strongly suggested that the improvement of the diabetes mellitus was related to secondary changes in the endocrine glands and particularly to the hyperplasia of the Langerhans islands.

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del Castillo, E. B. (*Buenos Aires, Argentina*): SYNDROME OF ANTERIOR HYPOPHYSIAL INSUFFICIENCY: DIAGNOSIS AND TREATMENT. Rev. Assoc. Med. Argent. *63*:51-55, March 15-30, 1954 (Abstr. in J.A.M.A. *156*: 744, Oct. 16, 1954).

The syndrome is associated with depression of the basal metabolic rate, diminution of the protein reserves, changes in the metabolism of carbohydrates, extreme sensitivity to insulin, and a tendency to the development of hypoglycemia. The treatment of hypoglycemic coma includes the giving of dextrose solution by intravenous route and the administration of saline solution, cortisone, and desoxycorticosterone, and placing the patient in a bath of warm water to prevent lowering of body temperature.

Caughey, J. E.: HYPOPITUITARISM AND SOME DISTURBANCE OF CONSCIOUSNESS ASSOCIATED WITH IT. Austra-

lasian Ann. Med. 3:26-36, February 1954 (Abstr. in J.A.M.A. 155:1188, July 24, 1954).

Usually some form of stress, such as infection, injury, surgery, anesthesia, hypnosis, hypoglycemia, exposure to cold, or low-oxygen tension, produced the coma. Patients with hypopituitarism are unduly susceptible to attacks of hypoglycemia with coma, which may be precipitated by very small doses of insulin.

Chesrow, Eugene J.; Bleyer, John M. (*Cook County Institutions, Oak Forest, Ill., Chicago Med. Sch., Chicago, Ill.*): THE GLUCOSE TOLERANCE TEST ON THE AGED. Geriatrics 9:276-82, June 1954.

An oral glucose tolerance test was made in 39 nonambulatory and 41 ambulatory patients between the ages of 60 and 109. The importance of prolonging the oral tolerance test for at least three hours in patients over 60 was demonstrated because of the delayed return of the curve to normal in old people. In borderline cases, it was believed that a normal intravenous glucose tolerance test together with the general clinical picture would help to differentiate non-pathological prolonged curves from those indicative of diabetes mellitus. In this series, lack of physical activity did not seem to have a decisive influence on the glucose tolerance curve. A high renal threshold was found in many instances. No substantial differences in glucose tolerance were found between males and females.

Collens, William S.; Banowitch, Morris M.; Colsky, Jacob (*Diabetic Res. Lab. & Med. Serv., Maimonides Hosp., Dept. of Med., State Univ. of New York, Coll. of Med., Brooklyn, N.Y.*): LIPOPROTEIN STUDIES IN DIABETICS WITH ARTERIOSCLEROTIC DISEASE. J.A.M.A. 155:814-17, June 26, 1954.

An analysis of the circulating lipoprotein aggregates of the S_f 12-20, S_f 20-100, standard S_f 0-12, and standard S_f 12-400 classes is presented in 57 diabetics with clearly defined arteriosclerotic disease. It is found that these components fall largely into categories described as normal by Gofman and his associates in those diabetics who are free of diabetic nephropathy. It would, therefore, appear that a clearly defined figure for the normal concentration of the variety of molecular aggregates of lipoproteins identified by means of the ultracentrifuge is not available at present. It is even possible that what we regard as normal figures may ultimately prove to be abnormally high.

Atherosclerotic disease can be present in the young without being clinically detected and found only at the autopsy table. The recent report of Enos and his co-workers stated that in autopsies of 300 soldiers killed in the Korean war, 77 per cent showed anatomic evidence of atherosclerotic disease of the coronary arteries, despite the fact that their average age was 22 years. These persons were totally without symptoms before death and yet showed intimal thickening and atheromatous deposits in the coronary arteries.

Colwell, Arthur R. (*Northwestern Univ. Med. Sch., Chicago, Ill.*): THE RATIONALE OF GOOD CONTROL IN DIABETES MELLITUS. J. Kentucky M.A. 51:238-43, June 1953.

In addition to the evidence presented by the behavior of sugar tolerance, infection, and vascular disease in the poorly controlled diabetic, common sense and logic should determine the policy of every thoughtful physician in this respect. It should not be necessary to present proof that abnormal conditions are harmful and normal ones preferable. Instead, proponents of lax therapeutic policies in diabetes should produce proof that abnormal conditions are harmless. Nothing of this sort is available. Until it is, every physician should maintain as nearly normal conditions in his diabetic patients as possible in the fear, if not the certainty, that not to do so will invite trouble.

The fact that some glycosuria is accepted in certain cases of severe diabetes should not encourage the allowance of it in milder diabetes where it is unnecessary and avoidable. The two things required by physicians to prevent it are, first, the conviction that it will lead to harm and, second, some attention to details of diet and insulin adjustment. The methods are available; all that is required is their thoughtful application in the nine out of ten diabetics who will profit from them. It is the author's belief that another generation of diabetics managed according to these principles will tell a different story about the inevitability of diabetic complications. The only reason this story is not apparent now is the fact that too few patients have tried to keep well-controlled and too many doctors have failed to encourage them to do so. Here is the opportunity to practice preventive medicine in a pure form. We have learned how to keep diabetics alive; now we must learn how to keep them well.

Copland, William A. (*United Bristol Hosp., Bristol, England*): BONE CHANGES IN DIABETES. Proc. Roy. Soc. Med. 47:345-47, May 1954.

Changes in the metatarsals and phalanges were studied at the diabetic clinic of the Bristol Royal Infirmary in cases of diabetes with symptoms or signs referable to the feet. The feet were X-rayed if there were features of diabetic neuritis (including increased or diminished sensation or absent tendon reflexes) gangrene, absent pulses, corns and ulcers.

The classical features of a Charcot joint were seen in none of the cases. An alternative explanation was therefore sought for the changes, and it was found that all the patients suffered or had suffered from an inflammatory lesion near the site of the affected bone. In most cases, this was in a perforating ulcer. In other cases, especially where the phalanges were involved, there was or had been a septic corn or cutaneous gangrene. In the latter condition, infection is of paramount importance. Although there is no reason why a true Charcot joint should not develop in a diabetic with neuritis, it is considered that the vast majority of bone changes commonly seen in this condition, although influenced by poor blood supply, lack of sensation, and possibly by the abnormal metabolism of diabetes, are the result of an inflammatory process. This explanation applies to a variety of other conditions affecting the extremities in which cutaneous lesions develop and are open to infection.

Duncan, John A. (*Univ. of Washington Sch. of Med., Swedish Hosp., Seattle, Wash.*): MANAGEMENT OF THE SURGICAL PATIENT HANDICAPPED BY CARDIAC, DIABETIC, OR RENAL DISEASE. S. Clin. North America 34:1265-70, October 1954.

The author briefly mentions the special consideration which must be given to diabetic patients undergoing surgery.

Dunlop, D. M. (*Univ. of Edinburgh, Scotland*): ARE DIABETIC DEGENERATIVE COMPLICATIONS PREVENTABLE? Brit. M. J. 2:383-85, Aug. 14, 1954.

The author reports on 167 diabetic patients with control classified as good (39), fair (53), or poor (75) depending on glycosuria. The incidences of retinopathy, cerebrovascular disease, nephropathy, and neuropathy were increased in those with poor control. The incidence of tuberculosis was the same in all 3 groups. The author believes that good control is essential and that the patient should visit his physician frequently.

Editorial (*Buenos Aires, Argentina*): ACTION OF INSULIN UPON GROWTH. Medicina, Buenos Aires 14:353-55, October 1954.

A review of the experimental work on the growth-promoting effect of insulin in hypophysectomized animals is made. In view of this work and a clinical work recently published by Conn (1953), it is possible to assume the existence of a somatotropic pituitary hormone which would stimulate the pancreas to release insulin. The somatotropic influence of insulin itself also seems evident. (Spanish)

Editorial (*Tavistock Square, London, England*): COMPLICATIONS OF DIABETES. Brit. M. J. 2:404, Aug. 14, 1954.

The complications of diabetes are of three types—acidosis, infections, and cardiovascular renal disease. The first two should be preventable or amenable to therapy. The third type accounts for 75 per cent of the deaths among diabetics. There are two schools of thought concerning dietary control. One group feels that dietary control cannot prevent the development of degenerative complications, while the other group feels that dietary control will delay the appearance of these complications. Although the present aim of therapy is to maintain normoglycemia, more research into the pathogenesis of degenerative complications is needed to settle the question.

Editorial (*Montreal, Canada*): DIABETES DETECTION. Union méd. Canada 83:1266-68, November 1954.

According to a diabetes detection service carried out in 1951, there were 75,000 known diabetics in Canada. However, on the basis of the prevalence of diabetes demonstrated in an Ontario community as 1.2 per cent, it may be assumed that the number of diabetics would come to 225,000 in the total 15 million population of Canada. (French)

Editorial (*London, England*): DIABETIC MICRO-ANGIOPATHY. Lancet 2:536-37, Sept. 11, 1954.

In diabetes mellitus, capillary changes are found in the retina and glomeruli of the kidneys. Recently, capillary changes have also been found in conjunctival vessels. The changes consist of vessel irregularity and dilatation with red-blood-cell aggregations. These observations were made in very early diabetes and in subjects with a family history only of diabetes. If these findings are confirmed, suspicion will be sowed on the precept that such vascular changes result from lax control.

Editorial (*160 St. Ronan St., New Haven, Conn.*): PRACTICAL POINTS ABOUT DIABETES. Connecticut M. J. *18*:909-10, November 1954.

The education of the diabetic must start with diet, urine testing, and insulin administration. Continually, each visit should include the study of the results of dietary indiscretions, insulin reactions, acidosis, care of skin and feet, and extend even to the complications which come with time. The early, careful, and continued control is the only hope of postponing the eventual complications of this chronic metabolic disturbance. The diabetic will take his handicap no more seriously than his physician and has no other source of learning about his variation from a normal life.

Filho, Salgado (*Rio de Janeiro, Brasil*): ASTHMA, INSULIN, AND DIABETES. Rev. brasil. med. *11*:363-64, May 1954.

Regardless of favorable reports in the past on the beneficial use of insulin shock for the treatment of asthma, there is no positive evidence at present which justifies such therapy. (Portuguese)

Foreign Letters (*Austria*): ACUTE MYOCARDIAL INFARCTION. J.A.M.A. *156*:190, Sept. 11, 1954.

In a series of cases of myocardial infarction in Austria, diabetes was present in 2.7 per cent of the men and 3 per cent of the women (compared with 10 per cent and 15 per cent in America). Acute coma or excessive insulin dosage can become dangerous in these cases. A history of excessive use of tobacco was elicited in 40 per cent of the men and 6 per cent of the women.

Fryers, G. R.; Paley, Ronald G.; Tunbridge, R. E. (*Dept. of Med., Univ. of Leeds, England*): THE DESIGN OF INSULIN TRIALS. A POLYLYSINE INSULIN. Lancet *2*:782-84, Oct. 16, 1954.

The authors discuss insulin therapeutic trials using a new-type insulin. They present a modification of the method of Izzo and Crump to include factors of interdaily variation and carry-over effects of long-acting insulins.

Gibertini, G.; Malaguti, G.; Porro, A.; Vecchiati, R. (*Surg. Clin., Univ. of Modena, Milano, Italy*): SOME ASPECTS OF BODY REACTION TO TRAUMA DURING HIBERNATION: I. CHANGES IN BLOOD SUGAR. Atti soc. lombardo sci. med. e biol. *9*:13-16, February-March 1954.

It has been demonstrated that hibernation has a strong inhibitory effect on the changes in blood sugar and glycolysis following trauma. (Italian)

Goldberg, Mary; Gilmour, D. (*Div. of Entomology, Commonwealth Scientific and Industrial Res. Organization, Canberra, Australia*): THE SUBSTRATE SPECIFICITY OF THE MAGNESIUM-ACTIVATED ADENOSINETRIPHOSPHATASE OF MUSCLE. Arch. Biochem. *51*:411-18, August 1954.

The magnesium-activated adenosinephosphatase of rat muscle was found to split two phosphate groups from both adenosine triphosphate (ATP) and inosine triphosphate (ITP). The order of activity against the substrates was ATP>ITP>>IDP>ADP. Other organic phosphates and pyrophosphates were not attacked. The addition of alternative substrates caused an alteration (usually a decrease) in the rate of evolution of orthophosphate from both ATP and ITP, but the evidence did not conform with the requirements for competitive inhibition between the substrates. A number of inhibitors were found to affect the activity of the enzyme against both ATP and ITP. It was concluded that the substrate specificity of the adenosinetriphosphatase was not restricted to the triphosphate grouping.

Haugen, H. N.; Blegen, E. M. (*Oslo City Hosps., Dept. Krohgstøtten, Oslo, Norway*): SOME CLINICAL OBSERVATIONS IN DIABETES MELLITUS. Acta. med. scandinav.

150:291-96, Nov. 30, 1954.

Two cases of diabetic renal disease are described. In both cases, a characteristic sediment was formed when the urine was allowed to stand a few hours. It was made up almost exclusively of epithelial, granular and waxy casts. One of the patients developed a reduced insulin requirement simultaneously with the renal complication.

Houssay, B. A.; Hartmann, L. F.; Cardeza, A. F. (*Inst. of Biology and Experimental Med., Buenos Aires, Argentina*): META-CORTICOID DIABETES IN THE DOG. Rev. Soc. argent. biol. 30:33-43, April-May 1954.

Prolonged treatment with high doses of cortisone and more easily with hydrocortisone can produce permanent diabetes in dogs with the pancreatic mass surgically reduced to 16 to 20 per cent. Diabetes was not obtained with intact normal pancreas. Diabetes (metacorticoid diabetes) persisted after discontinuance of treatment with those steroids. Hydropic degeneration of beta cells was found in the islets of the diabetic dogs. Hyperplasia of beta cells and of islets was found in nondiabetic dogs. (Spanish)

Hubble, Douglas (*Derbyshire Royal Infirmary, Derby City Hosp. and Derbyshire Hosp. for Sick Children, England*): INSULIN RESISTANCE. Brit. M. J. 2:1022-24, Oct. 30, 1954.

An unusual case of insulin resistance in an adolescent girl is presented wherein for two years the insulin dosage fluctuated to as high as 19,250 units daily. The resistance was greatest during the premenstrual phase. Complete studies of urinary 17-ketosteroids, 17-ketogenic steroids, estrogens, and pregnandiol revealed no abnormalities. Hexamethonium had no effect on insulin sensitivity. The patient died of sepsis from insulin abscesses. It is suggested that growth hormone may have been concerned in the insulin resistance.

Iannaccone, Angelo; Kornerup, Tore (*Dept. of Metabolic Res., Wenner-Gren's Inst. and Opthalmic Clin., Karoline Inst., Stockholm, Sweden*): PLASMA LIPIDS AND DIABETIC RETINOPATHY. Acta med. scandinav. *148*:411-16, May 14, 1954.

Total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio were determined on the blood plasma of 41 diabetics with retinopathy and 59 diabetics without retinopathy. In the diabetics with retinopathy, there was found a significant elevation of plasma total lipids. This observation is discussed in relation to the recent hypothesis of increased adrenal cortical activity in diabetic patients showing retinopathy.

Iannaccone, Angelo; Möllerström, Jakob (*Dept. of Metabolic Res., Wenner-Gren's Inst., Stockholms Högskola, and Hosp. of the Swedish Diabetes Foundation, Stockholm, Sweden*): PLASMA LIPIDS AND DIABETIC ATHEROSCLEROSIS. Acta med. scandinav. *148*:417-24, May 14, 1954.

Plasma total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio were determined in 35 unselected diabetics with evidence of atherosclerosis and 35 unselected diabetics without manifest atherosclerosis. No significant difference was found between the two groups. The age and sex of patients are important considerations when plasma lipid values are interpreted. In the present series, increasing age appears to be a more important factor than the duration of the diabetes in the development of atherosclerosis.

Jacobi, Harry G. (*111 East 80th St., New York, N. Y.*): THE FOOD CONSUMPTION OF JUVENILE DIABETICS. EVALUATION OF DIETS USED AT HOME AND AT SUMMER CAMP. Am. J. Clin. Nutrition 2:343-47, September-October 1954.

Though the prescribed diets of 120 children at home were close to those given at the 1951 summer camp of the New York Diabetes Association, it was found that most of the children consumed much more carbohydrate than their diet permitted. Twenty-nine per cent of this group followed a "free diet" at home, but were as content with the measured diet given at camp as with the "free diet" at home. The study showed that most of the children and their parents had not been given sufficient diet instruction.

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de Jesús Macias, José; Rodríquez, Rafael (*Mexico*): DIABETES AND TUBERCULOSIS. J.A.M.A. *156*:908, Oct. 30, 1954. (Discussion at a meeting of Nat. Inst. of Pneumonology held June 1954, Mexico City.)

Of 2,018 diabetic patients observed in the Hospital de Enfermedades de la Nutricion between 1947 and 1954, 31 had pulmonary tuberculosis. In this series, the percentage of diabetic patients with tuberculous complications is less than that found by other observers. This is strange in view of the fact that there is high incidence of pulmonary tuberculosis in Mexico. This can perhaps be explained by the fact that most of the diabetic patients in this study were over 40 years old, and that there is a greater number of patients who require less than 40 units of insulin daily for control. In foreign statistics, tuberculosis is found more often in diabetic patients less than 40 years old and it is twice as frequent in persons with severe diabetes who require large doses of insulin. Paradoxically, the diabetes improves as the pulmonary lesions advance. Although diabetes is more frequent in women than in men, pulmonary tuberculosis was more frequently associated with diabetes in men.

Joslin, Elliott P. (*Boston*): A RENAISSANCE OF THE CONTROL OF DIABETES. J.A.M.A. *156*:1584-85, Dec. 25, 1954.

The pioneers in dietary treatment of diabetes, Bouchardat, Cantani and Naunyn, stressed control. Insulin arrived and patients treated with insulin did so much better than ever before that relaxation in the management of the disease seemed harmless. Insulin hid the tragic symptoms and signs of the disease and thus allowed to develop insidiously the vascular complications that finally led to disaster. Attempts to prevent the progression of the disease and its complications received little consideration. The warning statistics of doctors schooled in the treatment of diabetes were decried, even though again and again they showed in statistical form that the ultimate end of the diabetic patient was governed not so much by the duration of the disease as by the type of treatment followed. Against this background of apostasy, therefore, it is heartening now to read of the advocacy of control of the disease by those who have witnessed the results of the lack of it. All are in agreement that easy-going treatment may be followed by disastrous results and that a return to strict diabetic control is indicated. Better treatment of diabetes should be universal. Diabetes should be controlled. The means are at our door. We cannot afford to have 85 per cent of patients begin to have disease of the kidney, heart, and brain and begin to grow blind after the disease has lasted only fifteen years. More emphasis must be laid on prevention of diabetes by banishing obesity. Rules for marriage should be tightened so as to lessen the influence of heredity. All glycosurias of pregnant women should be treated. As suggested by Hoet's experiments with animals, even a tendency to diabetes elicited by glucose tolerance tests during pregnancy, should be treated with diet and insulin so that the development of the disease in mother and offspring may be averted.

It is justifiable to conclude that through early recognition of glycosuria and hyperglycemia, their prompt correction and the institution of suitable rules of life may defer the onset of the actual disease for years or a lifetime. There is far too much nursing and far too little doctoring of the diabetic. It may be true that only one in ten of our patients is now eligible for a life expectancy medal for living longer with diabetes than expected to live without it and that only 54 in the world have been recognized as perfect after 25 years of the disease, but surely we doctors should be able to postpone the onset of complications until after fifteen years in more than 15 per cent of our cases. We should strive to have our patients live longer with the disease than the average nondiabetic person, because our group of patients is the one most under the doctor's eye. If we do not make them live longer, then the argument for routine health examinations falls flat.

Kaplan, E. H.; Kennedy, Jean; and Davis, Jane (*Rheumatic Fever Res. Inst., Northwestern Univ. Med. Sch., Chicago, Ill.*): EFFECTS OF SALICYLATE AND OTHER BENZOATES ON OXIDATIVE ENZYMES OF THE TRICARBOXYLIC ACID CYCLE IN RAT TISSUE HOMOGENATES. Arch. Biochem. *51*:47-61, July 1954.

The authors present evidence that salicylate and related compounds inhibit the Krebs cycle in kidney and liver homogenates. The oxidative enzymes inhibited to the greatest extent are a-ketoglutaric dehydrogenase and succinic dehydrogenase. Inhibition of the former is reversed by the presence of an excess of magnesium ions. The two enzymes also differ in the relative inhibitory effects of other substances chemically related to salicylate. Inhibition of oxidation of succinate is also reversible, but the factor which reverses this inhibition is unknown. When magnesium is present in excess, salicylate may enhance oxidative activity.

Kass, Arne; Voll, Artur; Aarseth, Sverre: DIABETES. J.A.M.A. *156*:272, Sept. 18, 1954. (*These studies pub. in*

Tidsskritt for don norske laegeforening, July 1, 1954.)

Some babies born to diabetic women seem perfectly fit at birth, but two or three days later develop cyanosis and collapse with signs of acute dilatation of the heart. Recent observations of Engleson and Bjorklund of Sweden have suggested that such fatal attacks may be due to the development of hypopotassemia. Kass has taken his cue from these observations and in the case of an infant who collapsed suddenly when 13 hours old, he found electrocardiographic evidence of hypopotassemia. He administered 0.5 gm. of potassium by stomach tube. The same dose was given on the third, fourth, and fifth days of life. The electrocardiographic manifestations disappeared within three hours of the first administration of potassium chloride.

In an article on diabetes and pregnancy, Voll concludes that the risk of inheritance of diabetes is so great that it would be well to discourage the marriage of two diabetics or of a diabetic with the child of another diabetic. Persons who contemplate marriage under these conditions are entitled to factual information if they are foresighted enough to consult a physician on the subject. Aarseth shows how, thanks to insulin, the mean age of diabetics admitted to Ullevaal Hospital has risen. Hanssen's study for the period 1936 to 1939 showed that about 50 per cent of Ullevaal's diabetics were over the age 61; whereas this was the case with 63 per cent of Aarseth's patients.

Koga, Mutuyosi (*Inst. of Physiol., Kumamoto Univ. Coll. of Med., Kumamoto, Japan*): ON THE RELATION BETWEEN THE HEMOLYSIS AND GLUCOSE METABOLISM. Kumamoto M. J. 5:116-19, March 1953.

Hemolysis of rabbit erythrocyte suspended in hypotonic Tyrode's solution was studied from the view point of glycolysis. Hemolysis was retarded by addition of glucose to the Tyrode's solution, and when monoiodoacetic acid (0.001M) or sodium fluoride (0.01 and 0.02M) was added, hemolysis was not prevented in the presence of glucose. Thus glycolysis protects the erythrocyte against hemolysis, by supplying energy either directly or indirectly for the maintenance of the cells.

Lazarus, Sydney S.; Volk, Bruno W.; and Goldner, Martin G. (*Div. of Labs. and Dept. of Med., Jewish San. and Hosp. for Chron. Dis., Brooklyn, N. Y.*): HYPERGLYCEMIC ACTION OF PANCREATIC EXTRACTS FROM DUCT-LIGATED, ALLOXANIZED AND COBALT-TREATED DOGS. Metabolism 3:449-55, September 1954.

Dogs and rabbits injected intravenously with pancreatic extract from duct-ligated, alloxanized and cobalt-treated dogs showed a transient but definite hyperglycemia. The effect was weaker than that obtained with extracts from alloxanized and alloxanized cobalt-treated dogs. The decreased activity may have been due to marked fibrosis in the acinar tissue. These observations suggest that the site of glucagon production has not yet been settled.

Lee, J. (*Dept. of Physiol., Charing Cross Hosp. Med. Sch., London, England*): A QUICK AND SIMPLE METHOD FOR BLOOD-SUGAR ESTIMATION. Brit. M. J. 2:1087-88, Nov. 6, 1954.

A simple method for blood sugar estimation is presented using the color change produced when glucose is heated with dinitrosalicylic acid in alkaline solution. The determination takes only 10 minutes and agrees fairly well with the Hagedorn and Jensen method.

Loos, Manfred (*2nd Med. Univ. Clin. Hamburg-Eppendorf and Dept. of Metabolic Res., Wenner-Gren's Inst., Stockholms Högskola, Sweden*): STUDIES IN THE UTILIZATION OF PENTOSES IN DIABETES. Acta med. scandinav. *148*:425-31, May 14, 1954.

Research on normal persons and on 63 diabetic patients showed that xyloses agreed with them in every respect without any accompanying symptoms on condition that one single dosage did not exceed 40 gm. and the total quantity administered does not exceed 80 gm. per day. Xylose is well resorbed and has a caloric value of 3.7 calories per gram. It may be well employed in cooking, and as regards sweetness it rates between cane sugar and dextrose; it is very similar to dextrose in taste. Taken at an average, 15 per cent of the xyloses are secreted with the urine. On the same basis of the same dosage of insulin and diet, comparative experiments with 40 gm. of glucosis and xyloses resulted in the following: favorable effect of the xyloses on the secretion of sugar in the sense of a prominent diminution as well as a favorable influence on the ketonuria. A phosphorization of the xyloses is assumed and documented by respective diagrams. The influence of vegetables on the diabetic's

assimilation by digestion is apparently due to pentoses contained in the vegetables. The possibility of a stimulating effect of the xyloses on the assimilation by digestion with its metabolism will be revealed.

Lynch, Matthew J. (*General Hosp., Sudbury, Ontario, Canada*): NEPHROSIS AND FAT EMBOLISM IN ACUTE HEMORRHAGIC PANCREATITIS. A.M.A. Arch. Int. Med. 94:709-17, November 1954.

One case of acute hemorrhagic pancreatitis is described in full; three similar cases are briefly outlined, as is also one case of focal acute pancreatitis of necrotizing type. In all cases, pronounced nephrosis was a striking pathologic finding. Two of the acute cases were investigated by frozen section fat-stain technic, and widespread fat embolization was revealed. This is believed to be the cause of the commonly occurring nephrotic renal damage in this disease, though it is conceded that circulating enzymes and toxic tissue products may contribute. A sixth case is described, in which sequelae of a remote attack of acute hemorrhagic pancreatitis were found. In this case severe interstitial renal fibrosis, tubular atrophy, and paratubular granular calcification are believed to represent the natural resolution of the acute renal lesion in hemorrhagic pancreatitis. However, it is likely that very few cases reach this end stage.

Manes, Luigi (*Naples, Italy*): INSULINS WITH PROLONGED ACTION. La Diagnosi 10:425-38, October 1954.

The time action of various insulin preparations depends on their solubility at the *p*H of body tissues. The combination insulin-hyaluronidase in a proportion of 3 mg. hyaluronidase per each 400 units of insulin provides a constant and complete absorption of insulin, prevents the appearance of local phenomena and improves insulin-resistance of a peripheral origin. (Italian)

Matthews, J. D.; Camb, B. A.; and Edin, M. B. (*Royal Infirmary, Edinburgh, Scotland*): VASCULAR DISEASE IN DIABETES MELLITUS. Lancet 2:573-75, Sept. 18, 1954.

The author has surveyed 545 diabetic patients of all ages and 574 nondiabetic patients over 50 years of age for vascular disease. Vascular degeneration was found in 53 per cent of the diabetic patients, of whom 21 per cent had retinopathy. Vascular disease increased with age, duration of diabetes, and insulin requirement. Retinopathy increased with duration of diabetes. Of 308 patients with "fair" control, 11 per cent had retinopathy and 6 per cent albuminuria. Of 237 patients with "poor" control 38 per cent had retinopathy and 19 per cent albuminuria.

Merivale, W. H. H.; Hunter, Richard A. (*Guy's Hosp. Med. Sch., London, England*): ABNORMAL GLUCOSE-TOLERANCE TESTS IN PATIENTS TREATED WITH SEDATIVE DRUGS. Lancet 2:939-42, Nov. 6, 1954.

Glucose tolerance tests were carried out in 16 patients addicted to barbiturates. Abnormalities which were found consisted of fasting hypoglycemia with little response to glucose, delayed response, abnormally elevated response, and prolonged response to glucose. The authors were unable to account for the abnormal responses other than to postulate causes such as starvation, abnormal gut absorption, or endocrine derangement.

Mosenthal, H. O. (*New York City*): PROBLEMS IN THE MANAGEMENT OF SEVERE DIABETES. Am. J. Digest. Dis. 19:121, April 1952 (Abstr. from Journal-Lancet 71:493-96, November 1951).

Mosenthal does not like to regard the amount of insulin required as the gauge of severe diabetes. He feels that severe cases are those with such complications as retinitis, nephritis, coronary thrombosis, or gangrene. Most of the paper is devoted to the control of blood sugar and glycosuria without polyuria or hypoglycemia, although the author alludes also to the maintenance of normal nutrition and the avoidance of "nerve tension." To illustrate the influence of fluctuations in blood sugar on visual acuity, Mosenthal cites a patient who suddenly complained of nearsightedness when he developed glycosuria but became visually normal on a diabetic diet. Hypoglycemia may result in cerebral hemorrhage and possible retinal bleeding. Insulin reactions should be avoided at all costs.

Muri, Jan (*Oppland County Hosp., Lillehammer, Norway*): DIABETIC NEPHROPATHY AND RETINOPATHY. Acta med. scandinav. 149:211-19, July 8, 1954.

Of 269 patients treated in the Oppland County Hospital for diabetes during the years 1939-1951 (inclusive) 84 had the disease begin before the age of 50 and have lived with diabetes for 10 to 30 years (average 15.6 years). Seventeen patients have nephropathy and/or retinitis. In two cases, the fundi have not been examined. Twelve patients were not traced. Fifty-three patients (63 per cent) have normal urine and normal eyegrounds. The frequency of complications increased with the duration of the disease; the age when diabetes was diagnosed was without importance. All of the patients are in the group whose diabetes is poorly controlled. The development of vascular complications in diabetics parallels in many ways the increasing problem of coronary diseases. Freedom from the mental stress connected with life in big cities and highly industrialized areas may, to a certain degree, have protected the diabetics in this typical countryside district of Norway from late diabetic complications, and more than offset the lack of control. The author is doubtful that much would be gained by burdening these patients with a rigid diabetic control.

Nagahama, Shintoku (*Dept. of Pathol., Niigata Univ. Sch. of Med., Niigata, Japan*): STUDIES ON THE INFLUENCE OF ADRENECTOMY AND HYPOPHYSECTOMY UPON ALLOXAN-DIABETES. Acta Medica et Biologica *1*:191-212, December 1953.

With 26 normal rabbits, 22 adrenalectomized rabbits, and 15 hypophysectomized rabbits as the subject of experiment, control experiment was performed on alloxan-diabetes following a past example. From the results obtained, it became clear that adrenalectomy and hypophysectomy inhibit, at least, the increase in blood sugar in alloxan-diabetes. It is assumed that several endocrine organs, especially the hypophyseo-adrenal system, have an important role in the development of insular diabetes.

Nerenberg, S. T. (*Dept. of Pathol. Asbury Methodist Hosp.; Univ. of Minnesota, Minneapolis, Minn.*): BETA GRANULES OF ISLETS OF LANGERHANS OF RAT. A.M.A. Arch. Path. 58:236-40, September 1954.

Using fetal and newborn rats, the author has studied the normal development of beta granules in the islets of Langerhans and the experimental conditions which affect their development.

He finds that the beta cells in the fetal rat pancreas first show appearance of granules on the twentieth day of gestation. The beta cells become fully granulated 24 hours after birth, 48 hours after their initial appearance. The beta granules appear relatively much later in the rat (late as in the third trimester) than in the human (the first trimester). The alpha cells become granulated 96 hours after birth.

Insulin given to pregnant rats does not affect the developing islets of Langerhans of the fetus but maternal rat diabetes mildly inhibits the development of the fetal beta granules.

The developing beta granules of the newborn rat do not appear to be affected by starvation, injected glucose or treatment with cortisone.

Paley, Ronald G. (*Dept. of Med., Univ. of Leeds, England*): THE DESIGN OF INSULIN TRIALS. INSULIN-ZINC SUSPENSION (LENTE). Lancet *2*:784-87, Oct. 16, 1954.

By using the insulin trial method of Fryers, the author tested insulin-zinc suspension (lente) in four cases of unstable diabetes. The suspensions (amorphous, crystalline, and mixtures) appeared to suffer from the same limitations as did other insulin preparations.

Read, Willard O.; and Fodden, John H. (*Depts. of Physiol. and Path., Univ. South Dakota Sch. of Med. Sciences, Vermillion, S. D.*): INFLUENCES OF SYNTHALIN A ON GLUCOSE ABSORPTION IN NORMAL AND EXPERIMENTAL DIABETIC ANIMALS. Metabolism *3*:456-61, September 1954.

Studies were carried out to evaluate the effects of Synthalin A (decamethylenediquanidine hydrochloride) on glucose absorption by the dog intestine following subcutaneous injection of 10 mg. per kg. of Synthalin A. Dogs made diabetic by alloxan and pancreatectomy failed to absorb glucose after but not before receiving Synthalin A. There was no failure on the part of normal dogs to absorb glucose after they had been given Synthalin A. In the presence of insulin, Synthalin A does not interfere with intestinal absorption of insulin.

Rodríguez Miñón, J. L.; Jiménez Díaz, C.; de Górgolas, R. (*Med. Clin. and Dept. of Physiol. Inst. for Med.*

Res., Univ. of Madrid, Spain): CHANGES IN CARBOHYDRATE TOLERANCE IN PATIENTS WITH RENAL DISEASE. Bull. Inst. M. Res. Univ. Madrid 6:97-104, April-September 1953.

An Exton-Rose glucose tolerance test was carried out in 14 cases of nephritic patients. Blood sugar determinations were carried out by means of Hagedorn-Jensen's method. A fasting hyperglycemia was found in 3 cases with values varying from 103 to 209. After the oral administration of glucose, a diabetic type of tolerance curve was demonstrated in 10 patients. These findings support the assumption that there is a disturbance in carbohydrate utilization in patients with nephritis, and would also confirm the experimental evidences of a renal participation in carbohydrate metabolism. (Spanish)

Rodríguez, R.; Casarín, R. E. (*Mexico City, Mexico*): ACIDOSIS AND DIABETIC COMA. Rev. invest. clin. 6:21-64, January-March 1954 (Abstr. in J.A.M.A. *156*:639, Oct. 9, 1954).

Diabetic acidosis in mature adults and in the elderly often stimulates uremia, alcoholic or barbiturate intoxication, cerebral trauma, or cerebral hemorrhage. A definite diagnosis was always feasible by demonstration of glycosuria and acetonuria. Complications observed at necropsy were: myocardial infarction, cerebral hemorrhage, pyelonephritis, acute meningitis, intestinal occlusion and bronchopneumonia from aspiration of vomitus. The authors point out the prognostic significance of acute dehydration in acidosis or diabetic coma as possible cause of renal dysfunction and consequent anuria.

Root, Howard F.; Pote, William H., Jr.; and Frehner, Hans (*Joslin Clinic, New England Deaconess Hosp., Boston, Mass.*): TRIOPATHY OF DIABETES. SEQUENCE OF NEUROPATHY, RETINOPATHY AND NEPHROPATHY IN ONE HUNDRED FIFTY-FIVE PATIENTS. A.M.A. Arch. Int. Med. *94*:931-41, December 1954.

In 155 cases of diabetes, a triopathy is presented consisting of the sequence of neuropathy, retinopathy, and nephropathy. Clinical, maternal, and hereditary etiologic factors are discussed. Until there is available more exact information regarding the basic biologic defects causing these diabetic sequelae, early and continuous attempts at control of diabetes by clinical methods are necessary if the lesions' triopathy are to be prevented or postponed.

Rooth, Gösta (*Med. Dept., Univ. Hosp., Lund, Sweden*): THE MORTALITY IN DIABETES MELLITUS IN SOME EUROPEAN COUNTRIES 1935-1949. Acta med. scandinav. *149*:65-74, June 12, 1954.

A study is reported of the mortality in diabetes mellitus per 100,000 living in Sweden, Norway, Denmark, Finland, Netherlands, and Switzerland in the years 1935 to 1949. In all these countries with the exception of Denmark, there has been a decrease in the diabetes mortality of about 40 per cent during the last years of the war as compared to the prewar level. The reason for this decrease lies probably in the rationing of food, which in Denmark was less severe than in the other countries. The apparently high diabetes mortality in Denmark is due to a different mode of registration as compared with the other countries studied.

Rowntree, Leonard G.; Poppiti, Robert J. (1342 *duPont Bldg., Miami, Florida*): DIABETES INSIPIDUS, DIABETES MELLITUS, AND INSULIN RESISTANCE WITH HISTOCYTOSIS. J.A.M.A. *156*:310-12, Sept. 25, 1954.

The coexistence of diabetes insipidus and diabetes mellitus is rare but the constantly increasing number of reported cases of coexistence of these two diseases makes mere chance appear an unlikely explanation of their relationship. The question arises whether it is possible to find an adequate pathological basis for both syndromes. A patient who was under clinical observation for seven years was treated successively and, with the passing of time, collectively, for diabetes mellitus, diabetes insipidus, intercurrent infections, and insulin resistance. The autopsy revealed marked bone marrow changes and the widespread invasion of tissue by lipid-containing and non-lipid-containing histocytes, which were found in the bone marrow, the posterior lobe of the pituitary gland, and other organs, and which resembled the cells in lipid histiocytosis of cholesterol type (Hand-Schüller-Christian disease).

Singer, H.; Sporn, J.; and Necheles, H. (*Dept. of Gastro-Intestinal Res., Med. Res. Inst. of Michael Reese Hosp., Chicago, Ill.*): FATTY ACID ABSORPTION AND CHYLOMICRONS. Science *118*:723-24, Dec. 11, 1953.

In a study of the absorption of oleic acid in the dog (a) after ingestion by the intact animal, (b) from a jejunal Thiery fistula, and (c) from a jejunal Thiery fis-

tula with sodium taurocholate as bile salt mixed with the oleic acid, the authors observed chylomicronemia in each instance, least marked in (a) and greatest in (c), implying that the absorption pathway from the intestinal tract is through the lymphatics and indicating that bile salt is not necessary for long-chain fatty acid absorption but enhances it.

Sloper, J. C. (*Bernard Baron Inst. of Pathol., London Hosp., London, England*): SMALL PANCREATIC ISLET ADENOMATA IN ADDISON'S DISEASE. REPORT OF TWO CASES WITH AN ANALYSIS OF ISLET SIZE IN THESE AND FOURTEEN OTHER CASES. A.M.A. Arch. Path. *58*:294-303, October 1954.

The author has made an intensive histological examination of the pancreas of 17 of 37 necropsies in cases of Addison's disease. The study was stimulated by a theory recently advanced by Hinerman that there is a possibility of an overproduction of insulin by the pancreas on the ground that there is in every case gross hyperplasia of islet tissue. The author was unable to confirm the contention that there is a gross hyperplasia of islet tissue in Addison's disease. Small islet adenomata were found in two cases, but there was no clinical or cytological evidence to suggest whether or not these were functioning. The author concludes that, at present, the tendency in this condition toward hypoglycemia should be regarded as extrapancreatic in origin.

Staub, A.; Sinn, L.; and Behrens, O. K. (*Lilly Res. Labs., Indianapolis, Ind.*): PURIFICATION AND CRYSTALLIZATION OF HYPERGLYCEMIC GLYCOGENOLYTIC FACTOR (HGF). Science *117*:628-29, June 5, 1953.

The authors present a preliminary report on the isolation of a crystalline material which is relatively insoluble in cold water, gives positive biuret, phenol reagent, and Sakaguchi tests, and the ultraviolet absorption curve shows a maximum at 278 *u* and a minimum at 250 *u*.

Svanborg, A.; Birke, G.; Plantin, L. O. (*King Gustaf V:s Research Inst. and Med. Clin., Karolinska sjukhuset, Sweden*): ADRENAL FUNCTION AND HYPERLIPEMIA IN NEPHROSIS AND DIABETIC NEPHROPATHY. Acta med. scandinav. *148*:73-76, Feb. 9, 1954.

Because it has been observed in certain instances that disturbances of the adrenal activity may affect lipid metabolism, an attempt was made to estimate the adrenal activity in five cases of nephrosis with grave hyperlipemia, in four cases of diabetic nephropathy, and in one dog with hyperlipemia following bilateral ligation of the ureters. This investigation does not support the theory that the cause of hyperlipemia in the diseases studied might be impaired adrenal activity. The Compound F concentration in all cases lay within normal limits. Fractionation of urinary 17-ketosteroids in two cases of nephrosis showed a normal steroid composition. In three of the cases of nephrosis, the Compound F concentration was determined both before and after administration of ACTH. In 2 of the cases of nephrosis, a poor adrenal response was obtained, such as is seen in some patients with severe, chronic diseases. In no case were results obtained that might indicate increased adrenal activity.

Tanaka, Ikuro (*Dept. of Physiol., Nagasaki Univ. Sch. of Med., Nagasaki, Japan*): IS THE ALLOXAN INITIAL HYPERGLYCEMIA IN RABBITS DUE TO THE AUGMENTED ADRENALINE SECRETION FROM THE ADRENALS? Kumamoto M. J. *6*:40-45, August 1953.

Two hundred milligrams of alloxan per kg. body weight was injected intravenously in 11 normal rabbits and 6 demedullated ones. The observed initial hyperglycemia after alloxan administration did not differ in both groups. Thus, it is unquestionable that the alloxan initial hyperglycemia is not connected with the adrenaline secretion from the adrenal glands.

Torres, Rafael; Concha, Luis; Cornejo, Laura; Hamuy, Yolanda (*Dept. of Psychiatric Res., Psychiatric Hosp., Santiago, Chile*): ACTION OF SODIUM GLUTAMATE AND NICOTINAMIDE UPON THE CEREBRAL CONSUMPTION OF GLUCOSE AND OXYGEN (A-V DIFFERENCE) DURING HYPOGLYCEMIC COMA. Rev. neuro-psiquiat. *17*:32-39, March 1954.

Sodium glutamate does not produce variation in the cerebral consumption of glucose, but it does increase oxygen consumption and elevates coma levels toward recovery from deeper comatose state. Nicotinamide did not produce any change in the cerebral consumption of glucose and oxygen. Moreover, it did not alter levels of coma. (Spanish)

Urteaga B. Oscar; Peralta, Aurelio (*Dept. of Pathol., Hosp. Dos de Mayo, Lima, Peru*): OBSERVATIONS ON TWO CASES OF PANCREATIC ISLET CELL ADENOMAS: HYPERINSULINISM PRESENT IN ONE OF THEM. Archivos Peruanos de Patologia y Clinica 8:337-45, Sept. 1954.

Postmortem examination of one of these cases revealed a large islet-cell tumor which did not produce any hypoglycemic symptoms in the patient. The magnitude of cellular proliferation was enough significantly; however, no symptoms were recorded. Disappearance of hypoglycemic crisis followed removal of the tumor in the second case. (Spanish)

Wickes, Ian G. (*North Middlesex Hosp. and Southeast Essex Group, England*): FOETAL DEFECTS FOLLOWING INSULIN COMA THERAPY IN EARLY PREGNANCY. Brit. M. J. 2:1029-30, Oct. 30, 1954.

A case is presented wherein a woman receiving insulin shock therapy for schizophrenia delivered a mentally defective child with hypertelorism and optic atrophy. A study of a small number of previously reported cases suggests that insulin may be injurious only when given before the tenth week.

Wise, George N. (*Dept. of Ophthal., New York Univ. Post-Graduate Med. Sch., New York, N. Y.*): OCULAR FINDINGS IN DIABETES. New York S. J. Med. 53:2182-84, Oct. 1, 1953.

The nature and mechanisms of the commonly encountered ocular complications of diabetes are discussed with emphasis on diabetic retinopathy.

Wynn, Victor (*St. Mary's Hosp. Med. Sch., London, England*): ELECTROLYTE DISTURBANCES ASSOCIATED WITH FAILURE TO METABOLISE GLUCOSE DURING HYPOTHERMIA. Lancet 2:575-78, Sept. 18, 1954.

The author has shown in hypothermia in one patient and five dogs that exogenous glucose is metabolised slowly. Intravenous glucose resulted in marked elevation of the plasma concentration of glucose with consequent extracellular space expansion and dilution of extracellular electrolytes.

Ziegler, Dewey K. (*Boston Psychopathic Hosp. and Dept. of Psychiatry, Harvard Med. Sch., Boston, Mass.*): MINOR NEUROLOGIC SIGNS AND SYMPTOMS FOLLOWING COMA THERAPY. J. Nerv. & Ment. Dis. 120:75-78, July-August 1954.

Twenty-two patients were given complete neurologic evaluation before and after a course of insulin-coma therapy. No marked changes were demonstrated in muscle power, deep tendon reflexes, or visual acuity. Seven patients showed some unsteadiness of gait following the course of treatment. Thirteen patients experienced paresthesias of some sort, following the course of treatment. Two of these showed a considerable degree of demonstrable sensory loss. The significance of the high incidence of paresthesias and their relation to a possible peripheral neuropathy or central nervous system lesion is discussed. The suggestion is offered that brain dysfunction is a common though unrecognized sequel of insulin coma treatment, accounting for some of what are now thought of as nonspecific symptoms.

EDITORIALS

CURRENT CONCEPTS OF BODY WEIGHT AND OBESITY

In 1940, Wells[1] published an article entitled, "Adipose Tissue, a Neglected Subject." He called attention to the failure of the medical profession to place proper emphasis on an important component of the body. Since then the situation has changed. In December 1953, Mayer[2] began an article by saying, "Obesity has become a national obsession." He referred to the propaganda for low caloric processed foods and drinks, for so-called comfortable weight reduction programs, and for various advertised nostrums and pills purported to ease the path toward normal weight. This propaganda has resulted in large measure from the increasing interest shown by the medical profession in the serious problem of obesity, particularly in relation to the hazards of cardiovascular-renal disease and diabetes mellitus.

In the intervening years, attention has been directed toward the metabolism of adipose tissue, methods of measuring the degree of obesity, and an assessment of the factors that lead to obesity. The latter two problems have recently been well reviewed in articles appearing in *Physiological Reviews*.

Keys and Brozek[3] reviewed the efforts that have been made to measure the absolute quantities of fat in the body. The body may be considered as containing two large components: the lean body mass and fat. The lean body mass has a fairly constant composition and is the metabolically most active component. Superimposed on the lean body mass are quantities of fat which may vary from 1 per cent to 40 per cent of the body weight. Obviously, measurements of the total body weight give no idea of the extent to which each of these components contributes to the composition of the body. Such information, however, is essential for accurate assessment of the role that body weight plays in the development of disease.

Direct analysis of the body composition, by its very nature, is not clinically feasible. In the past, indirect analyses have been notoriously unreliable or clinically impossible. The standard height-weight tables fail to reflect the significance of the lean body mass and may, in physically active individuals, suggest obesity when the percentage of fat may be well within the normal range. A new technic for the estimation of the fat component, clinically feasible although not popular as yet, is based upon the determination of the thickness of skin folds. Standard calipers have been devised and formulae developed by which the total body fat can be computed from the thickness of skin folds measured in certain areas, such as the mid upper arm, beneath the scapulae, and above the iliac crest. Within recent years, other technics have been developed for the determination of the lean body mass and/or the total body fat. These involve the calculation of the total body water by dilution methods, the estimation of the total body fat by use of fat-soluble indicators, or the determination of the total body density or specific gravity.

As a result of the use of such methods, alone or in combination, certain significant bits of information have been obtained. Body fat increases with age, even if the body weight remains constant. In other words, the lean body mass decreases gradually with age. The failure to recognize this and to decrease the caloric intake with age plays a definite role in the slow, steady increase in weight which is so common with increasing age. The "physiological fatness" of women has been demonstrated as occurring at all ages. The direct relationship of physical activity and the size of the lean body mass has been demonstrated and suggests the need for a reassessment of the concepts of the role played by physical activity in gain or loss of weight.

Mayer[4] approached the problem of obesity from the

[1] Wells, H. G.: Adipose tissue, a neglected subject. J.A.M.A. *114*:2177-83, June 1, and 2284-89, June 8, 1940.

[2] Mayer, J.: Multiple origins of obesity. Nutrition News *17*:5, Dec. 1953.

[3] Keys, A., and Brozek, J.: Body fat in adult man. Physiol. Rev. *33*:245-325, July 1953.

[4] Mayer, J.: Genetic, traumatic and environmental factors in the etiology of obesity. Physiol. Rev. *33*:472-508, Oct. 1953.

point of view of the genetic, traumatic, and environmental factors related to its development. While recognizing that, in the last analysis, an excess of caloric intake is always associated with the development of obesity, he emphasized that this alone gives little insight into the underlying disturbances. Emphasis on caloric balance has probably clouded the picture of the multiplicity of factors that may lead to an excessive intake and has resulted in a failure to evaluate properly the patient whose problem is excessive fat.

Experimental studies with the inherited obesity associated with a yellow strain in mice and with the inherited "hyperglycemic-obesity syndrome" in mice have called attention to the possibility of a genetic role in the obesity in man. The studies of Mayer with carbon-labeled acetate point to an inherited disturbance of acetate metabolism with a resultant increase in lipogenesis. No similar studies have been made in human obesity, but the possibility remains that an inherited enzymatic or hormonal defect could be present in certain instances.

The neuropsychiatric aspects of obesity are discussed. The association of obesity with experimental lesions of the autonomic nervous system, the hypothalamus, and the frontal lobes of the brain, calls attention to the possibility that disturbances in the neurovegetative system may lead to a train of events which end in overeating. The psychiatric aspects of the so-called "obesity-personality" are discussed with warning directed toward the danger of confusing causal with associated factors.

The significance of socio-economic factors is given its proper place. Food intake as a sign of prosperity and conviviality, and as a part of the celebration of important events in the life of the individual and family is emphasized. This paper also calls for a reassessment of the role of physical activities in the problem of overweight. It emphasizes that in the slow, steady increase in weight with age, the part played by decreasing physical activity without concomitant decrease in caloric intake must be given its proper consideration.

The importance of the problem of obesity in the United States cannot be overemphasized. To those who are concerned with this problem, a perusal of the papers by Keys and Brozek, and by Mayer will be helpful in evaluating the present status of the problem of determining who is fat and why. These papers cause one to wonder whether an excessive lean body mass carries the same penalty as excessive body fat. They should lead to a more careful distinction between overweight and overfat. And, very likely, they will increase the patience of those confronted with the problem of obesity by diverting their attention from the fact that the obese individual does overeat, or has overeaten, to a consideration of the factors that lead to his overindulgence in food.

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THE PREVALENCE OF OBESITY

Every doctor knows that obesity is common, but it is surprising to find that there is little published information regarding the present-day prevalence of overweight. As stated in a report prepared by the United States Public Health Service,* "There is no current information for the United States from which estimates of the prevalence of an excessive accumulation of fat in the body can be drawn."

The standard tables of heights and weights which have been most widely used are based on an investigation of the Association of Life Insurance Medical Directors and Actuarial Society of America published in 1912. For that investigation, data on height-weight relationships were collected on 221,819 men insured between 1885 and 1900 and on 136,504 women insured between 1885 and 1909. From these data, tables were prepared showing average weights for each inch of height for each five-year age group. It was not until recently that adequate attention has been given to the fact that standards based on height and weight alone are inaccurate indicators of overweight. Tables of "desirable weights" taking into consideration measurements of build and body type were developed by the Metropolitan Life Insurance Company in 1942 and 1943, and are now widely used. These tables show a range of weights for each inch of height according to the type of body frame. Consequently, the muscular man with heavy frame and sthenic build need not be compared with the slim individual of the same height but with lighter frame.

The limited data from four sources regarding the prevalence of overweight in the United States are presented in the report of the Public Health Service. These sources included a study of impairments among insurance examinees, insurance company estimates and observations made in multiple screening projects in Richmond, Virginia, and in Atlanta, Georgia.

The study conducted in 1938 by the Life Extension Institute among 10,000 life insurance policy holders (3,025 females and 6,975 males, aged ten years and over who were presumably free from illness) showed

*Estimated Prevalence of Overweight in the United States. 69:1084-86, Nov. 1954.

that 27.3 per cent (25.8 per cent of the males and 30.9 per cent of the females) were 10 per cent or more overweight. The estimates presented by the Metropolitan Life Insurance Company in 1942 and 1943 indicated that at least 20 per cent of the population over the age of thirty or about 15,000,000 persons, were 10 per cent or more overweight, and 6.7 per cent, or about 5,000,000, 12 per cent or more overweight. In the multiple screening project in Richmond, Virginia, conducted for six months in 1950 by the City Health Department in cooperation with the United States Public Health Service, it was found that 21.4 per cent of the screenees (33,799 persons aged 15 to 59 years who were presumably free from illness) were 10 per cent or more overweight and that 10 per cent were 20 per cent or more overweight. In a similar screening project conducted in 1950 by the Atlanta City and Georgia State Health Departments in co-operation with the United States Public Health Service, it was found that 24.8 per cent of the persons screened (182,207 persons aged 15 to 39) were 10 per cent or more overweight and 12.8 per cent were 20 per cent or more overweight. In both these screening projects a relatively higher percentage of Negro females than of white females were overweight. In the case of males there was a smaller percentage of difference in the same direction.

These observations made at different times and in different locations indicate that more than 20 per cent of the population of the United States are overweight (that is, 10 per cent or more above the standard weight for height, age and build); 6.7 to 12.8 per cent are 20 per cent or more above "desirable weight."

These statistical observations confirm the clinical observation of practicing physicians. In view of the etiological relationship of obesity to diabetes, it is evident that a high percentage of the persons susceptible to diabetes because of inheritance, are strongly exposed to a contributory factor which should be subject to correction.

HUMAN EXPERIMENTATION

At the close of World War II information was revealed concerning certain types of cruel and inhuman experimentation on men and women which had been carried on under the Hitler regime. Public opinion in this country and elsewhere was stirred to indignation. That doctors and scientists should have shown such disregard of human life had previously been considered unthinkable.

This problem has been considered by the World Medical Association, and at the annual meeting in Rome last fall its Committee on Medical Ethics formulated a set of guiding principles to be observed when experimentation is carried out on human beings. The text of these "principles" adopted by the General Assembly is as follows:

*Principles For Those in Research and Experimentation**

1. *Scientific and moral aspects of experimentation—The word experimentation applies not only to experimentation itself but also to the experimenter. An individual cannot and should not attempt any kind of experimentation. Scientific qualities are indisputable and must always be respected. Likewise there must be strict adherence to the general rules of respect of the individual.*
2. *Prudence and discretion in the publication of the first results of experimentation—This principle applies primarily to the medical press and we are proud to note that in the majority of cases this rule has been adhered to by the editors of our journals. Then there is the general press which does not in every instance have the same rules of prudence and discretion as the medical press. The World Medical Association draws attention to the detrimental effects of premature or unjustified statements. In the interests of the public each national association should consider methods of avoiding this danger.*
3. *Experimentation on healthy subjects—Every step must be taken in order to make sure that those who submit themselves to experimentation be fully informed. The paramount factor in experimentation on human beings is the responsibility of the research worker and not the willingness of the person submitting to the experiment.*
4. *Experimentation on sick subjects—Here it may be that in the presence of individual and desperate cases one may attempt an operation or treatment of a rather daring nature. Such exceptions will be rare and require the approval either of the person or his next of kin. In such a situation it is the doctor's conscience which will make the decision.*
5. *Necessity of informing the person who submits to experimentation of the nature of the experimentation, the reasons for the experiment and the risks involved—It should be required that each person who submits to experimentation be informed of the nature of, the reason for, and the risk of*

*World Medical Journal 2:12, Jan. 1955.

the proposed experiment. If the patient is irresponsible, consent should be obtained from the individual who is legally responsible for the individual. In both instances consent should be obtained in writing.

These proposals were discussed by delegates from Italy, Netherlands, Denmark, India, Burma, the United States and other countries. Agreement was reached in the Assembly and it was hoped that the principles would meet with the approval of physicians everywhere.

The efforts of the World Medical Association to set proper standards for human experimentation will be applauded. Any move that will ensure wise planning of experimental procedures and humane consideration of the subjects merits support. Yet the brief statements brought forth include puzzling and apparently irrelevant ideas. The proposal that "an individual cannot and should not attempt any kind of experimentation" seems strange and the statement regarding publicity appears to have no connection with the specific subject of human experimentation. The most important comment which might be made is that the essence of the statement of principles might be expressed more simply in terms of the golden rule—The conscientious research worker will not undertake any experiment on any man, woman or child unless he would be willing to have such an experiment performed on himself and on the members of his family.

BOOK REVIEWS

SIMPLIFIED DIABETIC MANAGEMENT. *By Joseph T. Beardwood, M.D., Professor of Diseases of Metabolism, Graduate School of Medicine, University of Pennsylvania, and Herbert T. Kelly, M.D., Associate in Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. Cloth, $3.00, pp. 194. J. B. Lippincott Co., Philadelphia and Montreal, November 1954.*

For a book, published in the highly competitive field of diabetic patient education, the appearance of six editions in a period of 20 years testifies to its usefulness. The present volume follows the format so successful in the former editions. The first chapter presents the history and general considerations concerning diabetes. The greater portion of the book is devoted to dietary management. As is well-known, the authors were pioneers in advocating more simplified dietary methods by the use of household measures. The basis of their system is the use of A and B units; the A unit represents five grams of carbohydrate and one gram of protein equal to 24 calories, while the B unit represents five grams of protein and ten grams of fat equal to 110 calories. The other parts of the book give a good discussion of insulin and its use, the complications of diabetes, diabetic hygiene, and laboratory tests. All are concisely and well presented. With so much emphasis on patient instruction, it is well that good textbooks such as this are available.

DIABETES MELLITUS, OBJECTIVES AND METHODS OF TREATMENT. *By Henry T. Ricketts, M.D., Professor of Medicine, University of Chicago, The School of Medicine, Chicago, Ill. $3.25, pp. 123, Charles C. Thomas, Publisher, Springfield, Ill., December 1954.*

This monograph on the treatment of diabetes is intended for the general practitioner. It does not pretend to be a complete treatise—for example, diabetes in pregnancy and in childhood are not considered—but it clearly aims to give the reader a practical guide to the management of the ordinary case of diabetes and of the difficulties that are commonly encountered.

A brief section is devoted to a discussion of objectives of treatment, among which are included preservation of whatever insulin-producing capacity the patient may have, and the prevention or postponement of the complications of diabetes. The relationship of the degree of control to the development of complications is treated in a thoughtful and convincing way. The second section deals with the management of diabetes in the office, with somewhat different approaches suggested for the "new" case, the previously treated patient and the "brittle" diabetic. Throughout this section the importance of careful control and thorough education of the patient are stressed. There are charts illustrating the time of action of the various insulins.

Other sections deal briefly but adequately with diabetic acidosis and with the management of diabetes in the surgical patient. A final section discusses the principles of diet prescription, and includes eleven sample diets based on the food exchange system now in common use. It is unfortunate that a section on the care of the feet is not included, and that the prevention and treatment of hypoglycemic episodes receive but scant attention.

The advocacy of a trial period on diet alone for all "new" cases may perhaps occasionally mislead the prac-

titioner into withholding insulin when it is urgently needed. The calculation of the caloric requirement of the individual patient, and its translation into an actual diet may seem rather cumbersome and mysterious to the average physician. Nevertheless, Dr. Ricketts' monograph contains a wealth of practical information, and reflects his wisdom and his wide experience in the field of diabetes. The book has a pleasantly informal style which makes it very readable, and his discussions of the physiology and pathology of diabetes are especially stimulating. It will be a valuable handbook for the general practitioner and the internist.

CLINICAL RESEARCH IN DIABETES AND PREGNANCY. *Edited by Jørgen Pedersen, M.D., Rigshospitalet, Copenhagen, Denmark. Pp. 48, Jørgen Pedersen, M.D., Copenhagen F, Denmark, 1954.*

This monograph edited by Pedersen presents the experience which he and his colleagues, Bente Bojsen-Miller, Hemming Poulsen, and Gunnar Jorgensen, have had in dealing with 205 pregnancies in 152 diabetic women. Among 156 pregnancies seen from 1926 to 1945, the fetal mortality was 38 per cent; among 49 pregnancies seen from 1946 to 1952, the fetal loss fell to 27 per cent. The fetal mortality varied from 12 per cent among patients who had long-term observation during pregnancy, to 36 per cent in short-term cases. Cesarean section was employed in 8 per cent of the deliveries. No hormones were administered.

Studies of the blood sugar of newborn infants of diabetic mothers showed no difference when compared with infants of nondiabetic mothers, except in cases given "short-term" observation and in cases in which there had been poor control of diabetes. No hypoglycemic levels were found. Glucose was not administered to newborn infants subsequent to 1945.

In regard to weight and length at birth, the infants of diabetic mothers were 550 gm. heavier and 1.5 inches longer than a control group of an equal number of infants of nondiabetic mothers. Excess size of the infant did not seem to be influenced by the number of pregnancies or by obesity in the mother. It was concluded that to a considerable degree the excess size was due to overgrowth or premature growth of the fetus and not represented merely by edema or obesity. It was seen more frequently in poorly controlled cases of diabetes or in cases in which it had been possible to give only short-term observation during pregnancy. If hyperglycemia in the latter part of pregnancy is a factor in the oversized infant it appears to be only one of several factors.

Hydramnios was frequently observed. The amount of amniotic fluid averaged 1,500 ml. in the "short-term" diabetic group, 1,000 ml. in "long-term" diabetics and 600 ml. in nondiabetics.

This monograph presents extensive carefully studied data. The conclusions correspond with current attitudes and practices. The findings support the opinion that the end results in any series of pregnant diabetics will be favorable in direct proportion as the patients are observed in their course directed throughout pregnancy by a team of professional attendants employing an established program.

Karl Petrén

A Leader in Pre-Insulin Dietary Therapy of Diabetes

*Russell M. Wilder, M.D.,**

Rochester, Minnesota

One of the most distinguished medical teachers and clinical investigators of his time was Karl Petrén. Some of his biographers have called him the most distinguished in Sweden. We know him in America principally because of his studies of diabetes and his advocacy in the very early nineteen twenties of a diet very high in fat. He was even more renowned, however, in neurology, and participated actively in Swedish public health affairs, notably in programs for the control of tuberculosis.

Born in 1868 of a line of clergymen on his mother's side, one of five brothers all of whom became outstanding, his medical training in Lund was followed by a year of study under the guidance of Dejerine, in Charcot's former clinic, the Salpétrière, in Paris. An equally lengthy sojourn was with Naunyn in Strassburg, then in Germany. He was called in 1902 to the professorship of internal medicine at Upsala and in 1910 to the chair of medicine in his alma mater, the University of Lund.

It was not until he took the professorship at Lund that Petrén's scientific interest was drawn to diabetes. Thereafter this became a major concern to him, largely because of dissatisfaction with the then current treatment by starvation. Extensive facilities and many patients with diabetes of severity, whom he could maintain for months and years under continuous supervision, enabled him to conduct extensive clinical and laboratory observations, employing various dietary procedures and ultimately arriving at conclusions of significance.

It is true that others, before Petrén, among them especially Weintraud, also a pupil of Naunyn, had found protein restriction to be beneficial in diabetes; but Petrén's studies went much further in revealing, as they did, that an increase of the nitrogen exchange would aggravate pre-existing acidosis, and that, with a rigidly restricted protein intake, even in patients with diabetes of severity, fat possessed a nitrogen sparing effect not much inferior to that possessed by carbohydrates in the normal. Thus the Petrén diet, as finally developed, became sufficiently high in fat to provide the calories required to maintain near normal body weight and this diet, to the surprise of everyone, could be tolerated without augmenting acidosis. Petrén's diets also were restricted in their carbohydrate content to that contained in leafy vegetables, and almost always, by these means, blood sugar levels, in chronic cases of severity, could be held near normal.

Because of the war (1914-1918) Petrén's early work on diabetes came to our attention late. The procedure, developed independently by Newburgh and Marsh,[1] closely resembled that which he was recommending; also, without knowledge at the time of Petrén's observations, I conducted a metabolic study with Boothby and Beeler,[2] and our findings were in support of his conclusions. His high fat diets were opposed, nevertheless, in many quarters and controversy raged until the discovery of insulin, in 1922, which soon permitted liberal diabetic diets and put an end to further need for such procedure. However, certain facts, brought to light by Petrén's studies and those of the others to whom I have referred, ought not to be forgotten: that fat like carbohydrate spares protein and that uncompensated acidosis, even when diabetes is severe, does not follow fat combustion if the nitrogen exchange is low and a minimal amount of carbohydrate is tolerated.

Petrén traveled widely and became an intimate of many of the foremost internists and neurologists in Germany, France, England and Scandinavia. He visited the United States and Canada before his death and left most pleasant memories of him here. Those who went to see him and his gracious wife, in their friendly home in

*Emeritus Member, Division of Medicine, Mayo Clinic, Rochester, Minnesota.

Lund, found a generous and charming host. He was a gourmet nonpareil. He loved good food and vintage wines; which explains perhaps his indignation at the starvation of the diabetic patients of the period.

Petrén was said by those who studied under him to have been a forceful teacher. I can well believe it, recalling as I do an apt analogy he drew between the defenses of the body and those of a European state, in danger always of sudden invasion by a foreign power. The buffers of the blood, bicarbonates and phosphates, are like the standing army of the state, ready for battle at a moment's notice; the ammonia mechanism, whereby the fixed bases of the blood are preserved in long-standing ketogenic acidosis, like the army of reserves, takes time to mobilize. Also, just as the country's army of reserves, its national army when mobilized, takes over and permits the standing army to be brought back to former strength, so too the carbon dioxide combining power of the blood, though depleted in the early combat with accumulating keto-acids, again may be restored to normal levels when the rate of mobilization of ammonia has been sufficiently increased.

Petrén was a fervent advocate of international cooperation, especially in the world of science. Following World War I he labored mightily to bring together, as promptly as might be, the colleagues from the opposing sides in that dreadful conflict. He nevertheless was a nationalist at heart, the civilized type of nationalist. I well recall his enthusiastic pleasure at the rolling landscapes of southeastern Minnesota. "Just like Sweden," he would say. "I have seen nothing so lovely since I left my home."

Petrén's magnum opus, his "Diabetes-studier," a volume of 1000 pages, published in Copenhagen in 1923, with his assistants, Smith, Otterström, Odin and Malmros, with a foreword by B. Naunyn, stands as a landmark, as Naunyn expressed it there, between two eras of research on diabetes.

REFERENCES

[1] Newburgh, L. H., and Marsh, P. L.: The use of a high fat diet in the treatment of diabetes mellitus. Arch. Int. Med. 26:647-62, Dec. 1920.

[2] Wilder, R. M., Boothby, W. M., and Beeler, Carol: Studies of the metabolism of diabetes. Jour. Biol. Chem. 51: 311-57, April 1922.

Program of the 15th Annual Meeting of the American Diabetes Association

June 4-5, Chalfonte-Haddon Hall, Atlantic City, N. J.

The American Diabetes Association takes pleasure in announcing that Professor Carl F. Cori, distinguished recipient of the Nobel Prize in Medicine and Physiology in 1948, will deliver the Banting Memorial Lecture at its Fifteenth Annual Meeting. His lecture, entitled "The Influence of Epinephrine and Glucagon on Enzyme Systems in Liver and Muscle," will be delivered at the Joint Meeting of the Association with The Endocrine Society on Saturday afternoon, June 4. Dr. Cori, Professor of Biochemistry, Washington University School of Medicine, St. Louis, will be presented with the Banting Medal at the Annual Banquet of the Association to be held that evening.

The program of the Fifteenth Annual Meeting includes these events, in addition to the Scientific Sessions which are published on the following pages:

Registration: Members and Nonmembers

June 3: 8:30 a.m.-7:00 p.m. (Office Floor), Haddon Hall
June 4: 8:30 a.m.-1:00 p.m. (Office Floor), Haddon Hall
1:00 p.m.-5:30 p.m. Carolina Room (Lounge Floor), Chalfonte
June 5: 8:30 a.m.-5:30 p.m. Vernon Room (Lounge Floor), Haddon Hall

Nonmembers Only

June 4: 1:00 p.m.-5:30 p.m. (Office Floor), Haddon Hall
June 5: 8:30 a.m.-5:30 p.m. (Office Floor), Haddon Hall

Social Hour: Saturday, June 4, 6:30 p.m. Garden Room (Lounge Floor), Haddon Hall

Banquet: Saturday, June 4, 7:15 p.m. Vernon Room (Lounge Floor), Haddon Hall

Annual Business Meeting: Sunday, June 5, 2:00 p.m.-2:30 p.m. Vernon Room (Lounge Floor), Haddon Hall

At the banquet on Saturday, June 4, Henry B. Mulholland, M. D., President of the American Diabetes Association, will speak. Following the presentation of the Banting Medal, there will be a response by Dr. Cori. A further highlight of the banquet will be an address, "Future Trends in Research," by Charles F. Kettering, Research Consultant and Director, General Motors Corporation.

The Board of Governors and Assembly of Delegates will convene for the second time at the Fifteenth Annual Meeting, their first meetings having been held in San Francisco in 1954 for the purpose of organization. This year they will function for the first time as deliberating bodies. As part of its agenda, the Assembly of Delegates will consider recommendations of the Council relative to closer financial and membership relationship between the Affiliate Associations and the National Organization.

SCIENTIFIC SESSION

Saturday, June 4, 2:00 p.m.

Joint Meeting with The Endocrine Society
Carolina Room (Lounge Floor), Chalfonte

HENRY B. MULHOLLAND and ALLAN T. KENYON, Presiding

Hypophysectomy in Severe Juvenile Diabetics: 18 Month Progress Report

LAURANCE W. KINSELL, LESTER LAWRENCE (by invitation), and ROBERT D. WEYAND (by invitation), Samuel Merritt Hospital and the Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

The Metabolism of C^{14}-Labeled Glucose in Normal and Diabetic Subjects

MAX MILLER, R. A. SHIPLEY, NOME BAKER (by invitation), W. W. SHREEVE (by invitation) and J. W. CRAIG (by invitation), School of Medicine, Western Reserve University, Lakeside Hospital, and the Radioisotope Unit, Veterans Administration Hospital, Cleveland, Ohio

Interactions of Growth Hormone, Cortisone and Tri-Iodothyronine in Experimental Diabetes in the Rat

J. A. OWEN, Jr., (by invitation), MORTON BOGDONOFF (by invitation) and FRANK L. ENGEL, Duke University School of Medicine, Durham, N. C.

BANTING MEMORIAL LECTURE

The Influence of Epinephrine and Glucagon on Enzyme Systems in Liver and Muscle

CARL F. CORI, Professor of Biochemistry, Washington University School of Medicine, St. Louis, Mo.

Effects of Glucose Levels on Lipogenesis and Oxidation in Rat Liver and Adipose Tissue

S. W. MILSTEIN (by invitation), and F. X. HANSBERGER (by invitation), Jefferson Medical College, Philadelphia, Pa.

The Distribution and Degradation of I^{131}-Labeled Insulin in Normals and Diabetics

GEORGE W. WELSH (by invitation), ELAINE D. HENLEY (by invitation), ROBERT H. WILLIAMS and NEIL J. ELGEE (by invitation), University of Washington School of Medicine, Seattle, Wash.

BANQUET

Saturday, June 4, 7:15 p.m.

Address by HENRY B. MULHOLLAND, President

Presentation of the Banting Medal to CARL F. CORI, Professor of Biochemistry, Washington University School of Medicine, St. Louis, Mo., and Nobel Prize Recipient in Medicine and Physiology, 1948

Response by CARL F. CORI

Presentation of the Banting Medal to EUGENE F. DuBOIS, Emeritus Professor of Physiology, Cornell University Medical College, New York, N. Y., by ELLIOTT P. JOSLIN, Honorary President, American Diabetes Association.

Address by MR. CHARLES F. KETTERING, Research Consultant and Director, General Motors Corporation, "Future Trends in Research."

SCIENTIFIC SESSION

Sunday, June 5, 9:00 a.m.

Vernon Room (Lounge Floor), Haddon Hall

HENRY B. MULHOLLAND, Presiding

A Simple Enzymatic Determination of Glucose Using Glucose Oxidase

R. E. FROESCH (by invitation), and A. E. RENOLD, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

Recent Insurance Mortality Experience on Persons with (1) Glycosuria and (2) Family History of Diabetes

MR. HERBERT H. MARKS, Manager, Insurance Medical Statistics, Metropolitan Life Insurance Company, and Chairman, Committee on Statistics, American Diabetes Association

Correlative Studies of Serum Lipids and Polysaccharides in Diabetes Mellitus

DAVID ADLERSBERG, College of Physicians and Surgeons, Columbia University and The Mount Sinai Hospital; CHUN-I WANG (by invitation), The Mount Sinai Hospital; HAROLD RIFKIN, JAMES BERKMAN (by invitation), College of Physicians and Surgeons, Columbia University, and the Montefiore Hospital; GEORGE ROSS (by invitation), and CLEMENT WEINSTEIN (by invitation), Montefiore Hospital, New York, N. Y.

Glomerular Changes and Steroid Diabetes Produced by the Administration of Various Adrenal Steroids, Whole Adrenal Extract and Corticotropin to Rabbits

J. M. B. BLOODWORTH, Jr., and GEORGE J. HAMWI, Ohio State University College of Medicine, Columbus, Ohio

Prosthetic Technics in the After-care of Diabetic Gangrene

EWEN DOWNIE, Alfred Hospital and University of Melbourne, Faculty of Medicine, Melbourne, Australia

Management of Kimmelsteil-Wilson Syndrome and Related Conditions

FREDERICK M. ALLEN, New York Polyclinic Medical School and Hospital, New York, N. Y.

PANEL DISCUSSION

Fluids and Electrolytes in Therapy

JOHN E. HOWARD, Moderator, Johns Hopkins University School of Medicine and John Hopkins Hospital, Baltimore, Md.

FRANCIS D. W. LUKENS, George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine, Philadelphia, Pa.

T. S. DANOWSKI, School of Medicine, The University of Pittsburgh, Pittsburgh, Pa.

RANDALL G. SPRAGUE, Mayo Clinic and Mayo Foundation Graduate School, University of Minnesota, Rochester, Minn.

HARVEY C. KNOWLES, Jr., University of Cincinnati College of Medicine, Cincinnati, Ohio

SCIENTIFIC SESSION

Sunday, June 5, 2:30 p.m.

Vernon Room (Lounge Floor), Haddon Hall

HENRY T. RICKETTS, Presiding

The Lente Insulins

K. HALLAS-MOLLER, Novo Terapeutisk Laboratorium, Copenhagen, Denmark

Lente Insulin: Clinical Evaluation in 109 Diabetic Patients

EDGAR A. HAUNZ, University of North Dakota School of Medicine and Grand Forks Clinic, Grand Forks, N. Dak.

The Relation of Portal Cirrhosis to Hemochromatosis and to Diabetes Mellitus

E. T. BELL, The Medical School, University of Minnesota, Minneapolis, Minn.

Steatorrhea Complicating Diabetes Mellitus with Neuropathy. Report of Cases Without Apparent External Pancreatic Insufficiency

KENNETH G. BERGE (by invitation), ERIC E. WOLLAEGER (by invitation), DONALD A. SCHOLZ (by invitation), E. DOUGLAS ROOKE (by invitation), and RANDALL G. SPRAGUE, Mayo Clinic and Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Juvenile Diabetes: Second Clinical Study of Twenty-Five Cases of Twenty-Five Years or More Duration

RANDOLPH P. PILLOW and LESTER J. PALMER, University of Washington School of Medicine and The Mason Clinic, Seattle, Wash.

PANEL DISCUSSION

What I Teach My Diabetic Patients

PRISCILLA WHITE, Moderator, Joslin Clinic, Boston, Mass.

BLAIR HOLCOMB, University of Oregon Medical School, Portland, Oreg.

EDWIN W. GATES, Niagara Falls Memorial and Mount Saint Mary's Hospitals, Niagara Falls, N. Y.

EDWIN L. RIPPY, University of Texas Southwestern Medical School and Baylor and Parkland Memorial Hospitals, Dallas, Tex.

GEORGE M. GUEST, University of Cincinnati College of Medicine and The Children's Hospital Research Foundation, Cincinnati, Ohio

BY TITLE

Glucagon as a Regulant of Insulin Function

GEORGE E. ANDERSON and ROBERT HILLMAN, State University of New York, College of Medicine, New York, N. Y.

Diabetic Neuropathy

JOSEPH I. GOODMAN, Western Reserve University School of Medicine and Mount Sinai Hospital, Cleveland, Ohio

Insulin Treatment of Diabetic Coma

ALBERT GRONBERG, Central Hospital, Vänersborg, Sweden

Differential Diagnosis of Renal Medullary Necrosis

GLENN W. IRWIN, FRANK VELLIOS (by invitation), ROBERT A. GARRETT (by invitation), Indiana University Medical Center, Indianapolis, Ind.

Blood Lipid Patterns in Diabetes Mellitus and their Relationship to Carbohydrate Metabolism

JOSEPH L. IZZO, ALFREDA G. SUSKIE, (by invitation), CECILIA KELLNER, (by invitation), University of Rochester, School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, N. Y.

Evaluation of Different Educational Approaches in the Class for Diabetic Patients

ALFARETTA C. JOHNSON, (by invitation), San Joaquin General Hospital, Stockton, Calif.

Diabetic Acidosis with Massive Hyperlipemia and Extensive Xanthoma Diabeticorum: Rapid Recovery and Control Under Massive Sugar Intake, Low Fats and Moderate Insulin Requirements

CARLOS P. LAMAR, University of Miami Medical School and Jackson Memorial Hospital, Miami, Fla.

The Use of Lente Insulin in Children

ROBERT A. LUSSKY (by invitation), ALVAH L. NEWCOMB, HOWARD S. TRAISMAN, Northwestern University Medical School, Children's Memorial Hospital, Chicago, and Evanston Hospital, Evanston, Ill.

Studies on Stable and Unstable Diabetics

E. PERRY McCULLAGH and JOHN G. ALIVISATOS (by invitation), Cleveland Clinic, Cleveland, Ohio

A Follow-up Study of Five Diabetes Detection Drives

HENRY E. OPPENHEIMER, St. Louis University School of Medicine and St. Mary's Group of Hospitals, and HAROLD K. ROBERTS, Washington University School of Medicine and Barnes and St. Luke's Hospitals, St. Louis, Mo.

Prolonged Administration of Vitamin B_{12}, Folic Acid and Calcium Pantothenate in Patients with Diabetes Mellitus

ELAINE P. RALLI, F. XAVIER BARBOSA (by invitation), MARY E. DUMM (by invitation), EDITH M. BECK (by invitation), BERTRAM LAKEN (by invitation), College of Medicine, New York University-Bellevue Medical Center, New York, N. Y.

Adrenal Cortical Function in Diabetes Mellitus

HAROLD RIFKIN, JAMES BERKMAN (by invitation), CLEMENT WEINSTEIN (by invitation), SEYMOUR LIEBERMAN (by invitation), Montefiore Hospital and College of Physicians and Surgeons, Columbia University, New York, N. Y.

Office Instruction of Diabetic Patients

GEORGE F. SCHMITT, School of Medicine, University of Miami and Mercy Hospital, Miami, Fla.

COMMITTEE AND OTHER MEETINGS

All events at Haddon Hall unless otherwise indicated

Monday, May 30

Executive Committee, 2:00 p.m.
Rowsley Room, Upper Lounge

Tuesday, May 31

Executive Committee, 9:00 a.m.
Rowsley Room, Upper Lounge

Wednesday, June 1

Executive Committee, 9:00 a.m.-12:00 noon
Room 134, Upper Lounge

Committee on Policies, 1:00 p.m.-5:00 p.m.
Card Room, Office Floor

Thursday, June 2

Committee on Finance, 10:00 a.m.-1:00 p.m.
Solarium, Lounge Floor

Committee on Professional Education, 10:00 a.m.-1:00 p.m.
Bakewell Room, Upper Lounge

Editorial Board, DIABETES, 2:00 p.m.-5:00 p.m.
Bakewell Room, Upper Lounge

Steering Committee of Committee on Detection and Education, 2:00 p.m.-5:00 p.m.
Room A, Lounge Floor

Joint Meeting of Editorial Board, DIABETES and Committee on Scientific Publications, 6:00 p.m.-7:30 p.m.
Mandarin Room, Tower Floor

Committee on Scientific Publications, 7:30 p m.
Room 134, Upper Lounge

Friday, June 3

Committee on Information for Diabetics, 8:00 a.m.-9:00 a.m.
Wedgewood Room 2, Lounge Floor

Council, 9:00 a.m.-12:30 p.m.
Card Room, Office Floor

Council, with Board of Governors, 1:00 p.m.-2:30 p.m.
Sun Porch, Lounge Floor

Council, 3:00 p.m.-5:30 p.m.
Card Room, Office Floor

Board of Governors, 3:00 p.m.-5:30 p.m.
Mandarin Room, Tower Floor

Committee on Employment, 6:00 p.m.-7:30 p.m.
Rowsley Room, Upper Lounge

Committee on Research and Fellowships, 6:00 p.m.-7:30 p.m.
Wedgewood Room 2, Lounge Floor

Assembly of Delegates, 7:30 p.m.
Music Room, Lounge Floor, Chalfonte

Saturday, June 4

Committee on Membership, 8:00 a.m.-9:00 a.m.
Wedgewood Room 2, Lounge Floor

Committee on Scientific Exhibits, 8:00 a.m.-9:00 a.m.
Wedgewood Room 2, Lounge Floor

Committee on Camps, 8:00 a.m.-9:00 a.m.
Rowsley Room, Upper Lounge

Council, 9:00 a.m.-12:00 noon
Card Room, Office Floor

Sunday, June 5

Editorial Board, ADA FORECAST, 8:00 a.m.-9:00 a.m.
Bakewell Room, Upper Lounge

Annual Business Meeting, 2:00 p.m.-2:30 p.m.
Vernon Room, Lounge Floor

Remarks by the President
Report of the Secretary
Report of the Treasurer
Report of the Executive Director
Summary of Committee Activities
Report of the Chairman, Nominating Committee
Election of Officers and Councilors
Installation of President-elect

Committee on Detection and Education, 7:00 p.m.
Rutland Room, Upper Lounge

POSTGRADUATE COURSE SERIES

The American Diabetes Association will conduct the Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems at the new Conrad Hilton Hotel in Dallas, Tex., Jan. 25-27, 1956.

The Third Postgraduate Course was held at the new Lankenau Hospital in Philadelphia, Pa., Jan. 19-21, 1955. This Course was directed by Edward L. Bortz, M.D., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, and Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pa. Henry F. Page, Jr., M.D., Instructor in Medicine, Jefferson Medical College, and Instructor in Medicine, Graduate School of the University of Pennsylvania, Philadelphia, Pa., was Associate Director.

Members of the Local Committee on Arrangements included Angelo P. Angelides, M.D., Joseph T. Beardwood, Jr., M.D., Edward S. Dillon, M.D., Garfield G. Duncan, M.D., W. Wallace Dyer, M.D., Francis D. W. Lukens, M.D., and Joyce T. Sheridan, M.D.

Although constructive criticism was also offered, evidence of the success of the Course is revealed in the comments of some of those who attended:

". . . discussion was excellent, concise and clearly understandable. I enjoyed the Course very much."

"General Summary, General Therapy, Minor Complications were the best. The ADA booklet for physicians is excellent and very helpful."

"I consider these Courses to be very helpful to the General Practitioner. I have greatly benefited by them."

"The plane of the subjects—just in advance of the basic—is satisfactory. I am always anxious to hear from our researchers and college professors. I was glad to note that purely investigational reports were omitted. I do suggest, however, that some inclusion of practical clinical talks be given by doctors who treat the patient."

"Highlight was 'The Young Diabetic.' It was practical and gave experimental data as well. Worth the whole lecture Course. I believe Postgraduate Courses should definitely give 'practical tips' as well as tell of the work being done. On the whole, a very successful Course."

Registrants expressed interest in subsequent reading of papers which were presented. Many of them will be published in future issues of DIABETES.

Physicians who attended numbered 176. Forty of them had previously attended the 1953 Course, twenty-one the 1954 Course, and nine all three Courses. (Attendance at the 1954 Course in Rochester, Minn., and the 1953 Course in Toronto, Canada, was restricted to 124 and 177 respectively, due to limited facilities.

The following is a registration breakdown for the Third Postgraduate Course, as well as a comparison with the two previous Courses:

	1955 Philadelphia	1954 Rochester	1953 Toronto
Members	135	83	93
Membership applications pending	23	24	23
Nonmembers	18	17	61
Total	176	124	177
Part-time registrants	2		
Graduate student	1	*	*
Fellows	3	*	*
Residents	10	*	*
Interns	5	*	*
Medical students	11	*	*
Guests	6		
Total	38	—	—
Grand Total	214	124	177
Additional Data			
Cancellations	15†	25	5
Applications rejected because of limited facilities	—	47	92
	1955 Philadelphia	1954 Rochester	1953 Toronto
Attendance at dinner	246	208	236

*Graduate Students, Fellows, Residents, Interns and Medical Students were not formally registered in 1954 and 1953, and there were a few in attendance.

†Two paid registrants did not attend or send in cancellations.

NEW INCOME TAX RULING

Physicians who wish to attend Postgraduate Courses offered by the American Diabetes Association will be interested in a recent ruling which provides for income-tax deductions for such purposes. The following is an excerpt from the Jan. 22, 1955, issue (page 371) of *The Journal of the American Medical Association*:

"*Postgraduate Courses*—Expenses incurred in attending postgraduate courses intended to keep a physician abreast of current developments in his area of competence are deductible. To qualify, the courses must be in the physician's field of practice and not designed to further his education so that he may embark on a new career or acquire a new status. Postgraduate expenses may include tuition, transportation, and meals and lodging if away from home. A physician who abandons his practice for an extended period of time to engage in study may not deduct his educational costs."

DIABETES WEEK 1955

Plans are now being formulated for Diabetes Week, November 13-19, which renews the year-round Detection Drive. Nearly all activities of the American Diabetes Association are conducted on the basis of the organizational year (from one Annual Meeting to the next). The Drive, major effort in health education and case finding, is conducted on a calendar year basis because Diabetes Week comes so early in the organizational year.

Louis K. Alpert, M.D., Washington, D.C., who last year succeeded John A. Reed, M.D., Washington, D.C., as Chairman of the Committee on Detection and Education, has accepted reappointment for 1955. Vice Chairmen include: Barnett Greenhouse, M.D., Hartford, Conn., Arnold Lazarow, M.D., Minneapolis, Minn., William H. Olmsted, M.D., St. Louis, Mo., John A. Reed, M.D., Washington, D.C. The following are Committee Members: J. Paul Aliff, M.D., Charleston, W. Va., Walter L. Anderson, M.D., Detroit, Mich., Robert H. Barnes, M.D., Seattle, Wash., Karl H. Beck, M.D., Wauwatosa, Wis., Morton E. Berk, M.D., Honolulu, Hawaii, Charles H. Best, M.D., Toronto, Canada, Donald R. Black, M.D., Kansas City, Mo., James F. Conner, M.D., Kecoughtan, Va., Richard C. Cullen, M.D., Denver, Colo., Manuel Gardberg, M.D., New Orleans, La., Joseph I. Goodman, M.D., Cleveland Heights, Ohio, Leo Goodman, M.D., Fresno, Calif., Robert C. Grauer, M.D., Pittsburgh, Pa., L. Harvey Hamff, M.D., Atlanta, Ga., Karl Hanson, M.D., Jacksonville, Fla., E. A. Haunz, M.D., Grand Forks, N. Dak., Jean M. Hawkes, M.D., Memphis, Tenn., Blair Holcomb, M.D., Portland, Oreg., Hugh Jeter, M.D., Oklahoma City, Okla., Robert L. Kesler, M.D., Oak Park, Ill., George K. Knowles, M.D., Hackensack, N. J., Harvey C. Knowles, M.D., Cincinnati, Ohio, William Kurstin, M.D., Washington, D. C., Carlos P. Lamar, M.D., Miami, Fla., Morris Margolin, M.D., Omaha, Nebr., Henry E. Marks, M.D., New York, N. Y., Carlisle Morse, M.D., Louisville, Ky., Joseph B. Cortesi, M.D., Schenectady, N. Y., Roy F. Perkins, M.D., Alhambra, Calif., Robert S. Radding, M.D., Houston, Tex., Edwin L. Rippy, M.D., Dallas, Tex., Howard F.

Root, M.D., Boston, Mass., George P. Rouse, Jr., M.D., Philadelphia, Pa., Thomas P. Sharkey, M.D., Dayton, Ohio, Leon S. Smelo, M.D., Birmingham, Ala., Howard E. Smith, M.D., Toledo, Ohio, Alfred T. Symmes, M.D., Indianapolis, Ind., Harold C. Torbert, M.D., San Diego, Calif., Frederick W. Ward, M.D., Easton, Pa., John R. Williams, Jr., M.D., Rochester, N. Y.

STUDENT SUBSCRIPTIONS

Medical Students, Interns and Residents may now subscribe to DIABETES at $4.50 per year, half of the regular subscription rate. This special price was recommended by the Committee on Scientific Publications, and accepted by the Council at the 1954-55 Interim Meeting in Philadelphia, Pa., Jan. 22-23, 1955.

SECOND CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

Henry T. Ricketts, M.D., First Vice President of the American Diabetes Association, has been named Official Delegate to the Second Congress of the International Diabetes Federation to be held in Cambridge, England, July 4-8, 1955. Many members of the ADA have made plans to attend, including a number of Councilors. A brochure containing information about reservations and so forth may be secured from the National Office of the American Diabetes Association.

CHANGE IN COMMITTEE NAME

The Committee on Research has been renamed the Committee on Research and Fellowships. This change in name was made upon recommendation of the Executive Committee at the 1954-55 Interim Council Meeting in Philadelphia, Pa., Jan. 22-23, 1955. Activities of the Committee on Research and Fellowships, for the time being at least, will be limited almost exclusively to the granting and awarding of Fellowships.

Coincidental with the change in Committee name, the General Research Activities Fund previously known as the Clinical and Research Fund has been changed to the Research and Fellowships Fund.

Research Fellowship application forms are available upon request. A full outline of the Fellowship program will be published in a future issue of DIABETES.

$7,500 RESEARCH GRANT AVAILABLE

The sum of $7,500, accepted by the Council of the American Diabetes Association from the Atlas Powder Company, is to be granted to individuals for research on the metabolism of sorbitol in the human diabetic. Those interested should submit their outline of research (personnel, physical facilities, etc.) to the Chairman of the Committee on Research and Fellowships of the American Diabetes Association. This Committee will select the recipient(s) of this grant.

New Members

The following Active Members were elected as of March 1 and April 1, 1955:

California	
Dittmann, Barbara E.	Berkeley
Fawell, William N.	Corona del Mar
Tufft, Robert W.	Oakland
Weeden, William F.	Oakland
Connecticut	
Ross, Allan M.	Darien
Tirella, Fred F.	Bristol
Delaware	
Dorph, Marvin H.	Wilmington
Pawley, Sigmund B.	Wilmington
Georgia	
Chelton, L. Guy	Atlanta
Knight, Arthur M., Jr.	Waycross
Illinois	
Highsmith, Ferris D.	Decatur
Roberts, Ralph C.	Evanston
Yeager, Leona B.	Chicago
Indiana	
Salon, Joel Warren	Fort Wayne
Iowa	
Erickson, Ernest D.	Sioux City
Kentucky	
Carter, Eugene S., Jr.	Mayfield
Louisiana	
Lovejoy, Harold B.	Maplewood
Mack, Sidney G.	Baton Rouge
Massachusetts	
Burrows, Ruth E.	Boston
Vance, Vernon K.	Boston
Michigan	
Dube, Arthur H.	Ann Arbor
Gittler, Robert D.	Ann Arbor
Peebles-Meyers, Marjorie	Detroit
Minnesota	
Loftus, Lawrence R.	Rochester

New Jersey	
Mazur, Edward F.	Camden
Trippe, Morton F.	Asbury Park
New York	
Adams, Vincent J.	Forest Hills
Appelman, David H.	Brooklyn
Falkson, Frederick	Walden
Gelfand, Maxwell L.	New York City
Goodkin, Louis	New York City
Mackowski, Herbert W.	Rochester
Millett, Joseph	Hempstead
Pisa, Joseph J.	Buffalo
Ray, Vincent R.	Garden City
Segaul, Herman J.	Utica
Woiff, Eugene F.	Newburgh
Ohio	
Fleisch, Kurt J.	Newark
Wolff, Adolf	Chillicothe
Pennsylvania	
Butters, J. Guy	Corry
Cooper, Herbert K.	Lancaster
Corson, Margaret L.	Hughesville
Degling, Erwin G.	Lewisburg
Margolis, Elliot J.	Levittown
McGhee, Saylor John	Lock Haven
Pringle, Robert W.	Pittsburgh
Rack, Morris A.	McKeesport
Wilcox, Homer B., Jr.	Philadelphia
Yarnall, George W.	Harrisburg
Rhode Island	
Rossignoli, Vincent P.	Providence
Texas	
Hoaglin, Lester L., Jr.	Houston
Virginia	
McCue, Frank A.	Richlands
West Virginia	
Ashton, Dudley C.	Beckley
Henson, Waldo C.	Charleston

OTHER COUNTRIES

Argentina	
Montagna, Carlos P.	Buenos Aires

The following Associate Member was transferred to Active Membership as of Apr. 1, 1955:

Oklahoma	
Hohl, James F.	Ada

News of Affiliate Associations

The CONNECTICUT DIABETES ASSOCIATION will hold its Seventh Annual Meeting April 28, beginning at 3:30 p.m., at Stratford, Connecticut. Henry Dolger, M.D., Associate Attending Physician for Metabolic Diseases and Physician in Charge of Diabetic Clinic, Mount Sinai Hospital, will be the guest lecturer. His topic is "Fructose in Diabetic Emergencies."

The NEW JERSEY DIABETES ASSOCIATION will hold its Third Clinical Society Meeting 1954-55 Session (Section on Metabolism, Medical Society of New Jersey) April 20, beginning at 9:30 a.m., at the Hotel Ambassador in Atlantic City. Garfield G. Duncan, M.D., will present "The Problem of Obesity"; William A. Nyiri, M.D., "Insulin in Clinical Medicine"; Herbert S. Kupperman, M.D., "Extrapancreatic Diabetes"; Victor A. Bressler, M.D., "Hepatic Coma in Portal Cirrhosis." The Clinical Society of the New Jersey Diabetes Association will hold a dinner meeting May 11, at Essex House in Newark, at which short papers and interesting case reports will be presented by its membership.

The New Jersey Diabetes Association is offering the J. Fred Johnson Award of $150 for the best essay submitted on problems relating to diabetes mellitus. Essays may cover either clinical or research investigations, and may include original studies or unusual case reports with suitable and complete comments. The presentation should not exceed 3,000 words. Submitted in double-spaced typewritten copy, in duplicate, it must reach the Award Committee at 91 Lincoln Park, Newark, no later than June 1, 1955. Candidates are restricted to residents or interns in New Jersey hospitals, or to New Jersey physicians in practice no longer than five years.

This Award was made possible through the generosity of the late J. Fred Johnson who wished to stimulate the interest of young physicians in this disease.

Newly elected officers of the New Jersey Diabetes Association include: Everett O. Bauman, M.D., President; Otto Brandman, M.D., Vice President; William Levison, M.D., Secretary; John J. Torppey, M.D., Treasurer. Clinical Society Officers are Joseph Skwirsky, M.D., Chairman, and Louis Grunt, M.D., Secretary. George A. Hess, M.D., Lewis I. Schwartz, M.D., and Marshall I. Hewitt, M.D., are members of the Board of Governors.

The TEXAS DIABETES ASSOCIATION will hold its Annual Meeting in Fort Worth April 24, 1955, at which the following program will be presented: "Presentation of Material Used in Out-Patient Management of Illiterate and Semi-literate, Low Income Diabetics," by Elizabeth C. Thomason, M.D., and John Chriss, M.D.; "The Diagnosis and Treatment of Pre-Diabetes," by Frank N. Allan, M.D.; "An Evaluation of Clinical Laboratory Methods in the Diagnosis and Management of Diabetes" by Charles Ashworth, M.D.; "The Function of Insulin" by Arthur Grollman, M.D.; "Clinical Observations on Allergic Sensitivity to Insulin," by Harvey B. Snyder, M.D.; Panel Discussion: "Diabetes and Pregnancy"; by George M. Jones, M.D., Frank N. Allan, M.D., James A. Greene, M.D., Donald M. Paton, M.D., William F. Mengert, M.D.; "Encephalopathy Due to Hypoglycemia" by Capt. James A. Gelinas, M.C.; "Lipoprotein Studies in Diabetes" by Harold Dobson, M.D.; "Diabetes Insipidus with Diabetes Mellitus, with Case Presentation," by Capt. James A. Ewart, M.C.; "The Role of Potassium in Diabetes" by Donald Seldin, M.D.; "Late Complications of Diabetes," by Frank N. Allan, M.D.

News Notes

Dr. Joslin to Give Banting Lecture in England

Elliott P. Joslin, M.D., Honorary President, American Diabetes Association, and Honorary President with Charles H. Best, M.D., International Diabetes Federation, will give the Banting Memorial Lecture of the British Diabetic Association in Cambridge, England, July 4, at 3:30 p.m. The Lecture, entitled "Diabetes for Diabetics," coincides with the opening day of the Second Congress of the International Diabetes Federation, which will be held in the same city.

Dr. Downie to Deliver Banting Lecture in Toronto

Ewen Downie, M.D., Melbourne, Australia, will give this year's Banting Lecture of the University of Toronto, May 16, at 5:00 p.m. His subject is "The Clinical Approach to the Problem of Diabetes Mellitus."

Dr. Downie is Dean of the Alfred Hospital Medical School in the University of Melbourne and is Senior Honorary Physician on the staff of that hospital.

On June 5, at the Fifteenth Annual Meeting of the American Diabetes Association, Dr. Downie will give a paper on "Prosthetic Techniques in the After-care of Diabetic Gangrene." He will also attend the Second Congress of the International Diabetes Federation at Cambridge, England, early in July.

Copies of Dr. Allen's Book on *Glycosuria and Diabetes* Still Available

Studies Concerning Glycosuria and Diabetes, by Frederick M. Allen, M.D., published by the Harvard University Press in 1913, is still available. Copies may be obtained without charge through the courtesy of a $1,000 grant from Eli Lilly and Company.

The book describes the production of diabetes by partial pancreatectomy, the first experimental production of hydropic degeneration of pancreatic islands and other early experimentations.

In view of the importance of the book for historic and reference purposes, preference will be given first to libraries and then to interested individuals. Requests for the book should be sent to Mr. J. Richard Connelly, Executive Director, at the National Office.

Third International Vitamin E-Congress

The 3rd International Congress for the study of Vitamin E will be held in Venice, Italy, from Sept. 5-8, 1955, in the premises of the Cini Foundation on the Island of San Giorgio Maggiore. Reports on experimental study and papers on clinical investigation will be presented. Information regarding the Congress and application for enrollment should be addressed to the Secretary's Office, 3rd International Vitamin E-Congress, Via Pietro Verri 4, Milano, Italy.

Personals

JEROME W. CONN, M.D., Professor of Internal Medicine and Director, Division of Endocrinology and Metabolism, and the Metabolic Research Laboratory, School of Medicine, University of Michigan, has been appointed Endocrinology Editorial Specialty Advisor for *Current Medical Digest.*

JEROME W. CONN, M.D., Ann Arbor, Mich., JAMES A. GREENE, M.D., Houston, Tex., GEORGE H. CURFMAN, JR., M.D., Denver, Colo., and WILLIAM A. H. RETTBERG, M.D., Denver, Colo., will be among the Officers of Instruction at the postgraduate course on "Fundamental Advances in Internal Medicine," arranged by the

American College of Physicians and scheduled for June 13-17 at the University of Colorado School of Medicine, Denver, Colo. DRS. CURFMAN and RETTBERG will participate in a panel discussion on "Hematologic Aspects of Collagen Diseases with Special Reference to LE-Cells with Rheumatic Diseases." DR. CONN will speak on "Aldosterone and Its Clinical Implications," and "Differential Diagnosis and Management of Spontaneous Hypoglycemia." DR. GREENE will talk on "Hypoproteinemia," and "Selection of Types of Insulin in Diabetes Mellitus."

GARFIELD G. DUNCAN, M.D., Philadelphia, will be an Officer of Instruction at the postgraduate course on "The Early Detection and Prevention of Disease," arranged by the American College of Physicians at the University of Pennsylvania School of Medicine March 28-April 1. His subject will be "The Prevention of Diabetes and Its Complications."

GARFIELD G. DUNCAN, M.D., recently participated in the International Medical Assembly of Southwest Texas in San Antonio, giving lectures on "Diabetic Management in General Practice," "Newer Insulin Preparations," and "Treatment of Hypertension." Dr. Duncan also participated in a panel discussion dealing with "Diseases of the Gall Bladder and Complications of Diabetes."

JOSEPH P. HOET, M.D., Ph.D., Professor of Clinical Medicine, University of Louvain, Belgium, will speak on "The Diabetogenic Action of Pregnancy" on March 15, at a combined meeting of the New York Academy of Medicine (Section on Medicine) and the Clinical Society of the New York Diabetes Association. Discussion will be by ALFRED E. FISCHER, M.D., and HUGH L. C. WILKERSON, M.D. EDWARD TOLSTOI, M.D., is Chairman and CHARLES A. POINDEXTER, M.D., Secretary of the Section on Medicine. MURRAY M. LEVITES, M.D., is Chairman of the Clinical Society, and LAWRENCE E. HINKLE, JR., M.D., Secretary-Treasurer. IRVING GRAEF, M.D., is Chairman of the Committee on Professional Education.

F. RAYMOND KEATING, JR., M.D., Rochester, Minn., FRANCIS D. W. LUKENS, M.D., Philadelphia, EDWARD H. RYNEARSON, M.D., and RANDALL G. SPRAGUE, M.D., both of Rochester, Minn., will be Officers of Instruction at the postgraduate course in "Selected Subjects in Internal Medicine," arranged by the American College of Physicians May 9-13, at the Mayo Clinic and Mayo Foundation. DR. RYNEARSON will be chairman at the welcoming ceremonies at the May 9 morning session. DR. SPRAGUE, who will be chairman of the afternoon session, will speak on "Problems in the Recognition and Treatment of the Causative Lesion in Cushing's Syndrome." DR. LUKENS will speak on "Comments on the Pathogenesis of Diabetes," and with Members of the Section of Metabolism will take part in a panel discussion on "Diabetes."

HARVEY C. KNOWLES, JR., M.D., and CECIL STRIKER, M.D., Cincinnati, will be Officers of Instruction at the postgraduate course in "Internal Medicine: Selected Topics," arranged by the American College of Physicians and scheduled for May 23-27 at the University of Cincinnati College of Medicine. DR. KNOWLES will speak on "Present Concepts of Sodium and Potassium Metabolism," and will participate in the "Conference on Hypertension and Electrolytes." DR. STRIKER will speak on "The Management of Complications of Diabetes Mellitus."

ARNOLD LAZAROW, M.D., Minneapolis, Minn., E. PERRY MCCULLAGH, M.D., ROBERT W. SCHNEIDER, M.D., and PENN G. SKILLERN, M.D., all three of Cleveland, Ohio, will be Officers of Instruction for the postgraduate course in "Pathology and Pathologic Physiology in Internal Medicine," to be held March 21-26 at The Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation. The course has been arranged by the American College of Physicians. DR. SKILLERN will take part in a Pathology Conference, "Diseases of the Pancreas," and will talk on "Hypoglycemia," and "Myxedema." DR. LAZAROW will talk on "Principal Pathways of Intermediary Metabolism" and "Experimental Diabetes." DR. SCHNEIDER will speak on "Hyperparathyroidism—Primary and Secondary," and "Therapeutic Effects of Estrogens and Androgens." DR. MCCULLAGH'S subjects will be "Management of Diabetic Acidosis and Coma," and "Disturbances of Adrenal Cortical Function."

E. PERRY MCCULLAGH, M.D., will speak at the Third Annual Scientific Assembly of the West Virginia Academy of General Practice which convenes in Charleston, April 16-17.

THOMAS H. MCGAVACK, M.D., is Chairman of the Local Arrangements Committee for the 1955 Annual Meeting of the American Geriatrics Society to be held at the Hotel Roosevelt in New York City April 21-22. Members of the American Diabetes Association scheduled to take part in the program include: Panel on Diabetes in the Aged: LAURANCE W. KINSELL, M.D., Moderator; Collaborators: HOWARD ROOT, M.D., THOMAS H. MCGAVACK, M.D., HERBERT POLLACK, M.D., EDWARD TOLSTOI, M.D. THOMAS H. MCGAVACK, M.D., will preside at an April 22 Morning Session, and will present "Urinary 17-Ketosteroid Excretion as Influenced by Age and Disease." LAURANCE W. KINSELL, M.D., will preside in a Panel on Cancer at the Afternoon Session. CHESTER SOLEZ, M.D., is author of a paper read by title: "Premature Vascular Degeneration in Diabetes Mellitus—Pathogenesis and Relation to Aging."

HENRY T. RICKETTS, M.D., Professor of Medicine at the University of Chicago, will give the Kellogg Lecture March 28 at the George Washington University Medical Center, Washington, D.C. His subject will be "The Vascular Problems of Diabetes."

The following members of the American Diabetes Association will participate in the Thirty-Sixth Annual Session of the American College of Physicians, to be held in Convention Hall, Philadelphia, Pa., April 25-29: EDWARD L. BORTZ, M.D., and GARFIELD G. DUNCAN, M.D., Philadelphia, are members of the Committee on Arrangements. FRANCIS C. DOHAN is a member of the Committee on Auditorium. DR. BORTZ is Chairman and HENRY F. PAGE, M.D., a member of the Committee on Entertainment. FERDINAND FETTER, M.D., and PERRY SCOTT MACNEAL, M.D., are members of the Committee on Hospital Clinics; and JOSEPH T. BEARDWOOD, JR., M.D., and NORMAN G. SCHNEEBERG, M.D., are members of the Committee on Panel Discussions, with GARFIELD G. DUNCAN, M.D., Chairman. CHARLES R. SHUMAN, M.D., is a member of the Committee on Publicity, and DR. DUNCAN is on the Committee on Technical Exhibits.

ERNEST M. BROWN, JR., M.D., will speak on "Hyperadrenocorticism," as part of the Hospital Clinic Program on April 28 at the Hospital of the University of Pennsylvania.

ARTHUR R. COLWELL, SR., M.D., will be moderator at a conference on "Diabetes," April 28 in Convention Hall. Others participating in the conference will be FRANK N. ALLAN, M.D., JOSEPH T. BEARDWOOD, JR., M.D., E. PERRY MCCULLAGH, M.D., and L. O. UNDERDAHL, M.D. DR. BEARDWOOD will also speak on "Newer Treatment of Diabetic Retinitis with Demonstrations," at Graduate Hospital of the University of Pennsylvania, April 26. DR. MCCULLAGH will speak on "On the Choice of Treatment for Hyperthyroidism" at Convention Hall April 26.

JEROME W. CONN, M.D., and WALTER LYON BLOOM, M.D., will participate Wednesday, April 27, at Convention Hall, when DR. CONN will talk on "Primary Aldosteronism, A New Clinical Syndrome." DR. BLOOM's talk will be on "Clinical Aspects of Plasma Volume Expansion."

T. S. DANOWSKI, M.D., will speak on "The Clinical Significance of the Low Salt Syndrome" April 25.

GARFIELD G. DUNCAN, M.D., will be moderator at a conference on "Hypertension" April 27, as part of the Panel Discussions and Clinical-Pathological Conferences. At the United States Naval Hospital on April 28, he will speak on "Diagnosis and Treatment of Addison's Disease Associated with Hyperglycemia." DR. DUNCAN will also moderate a "Clinical-Pathological Conference—Case II, April 29. ALEX M. BURGESS, M.D., will participate in the conference "Infections of the Kidney" April 27, and will take part in the "Clinical-Pathological Conference—Case I" April 29.

GEORGE M. JONES, M.D., will participate in a conference on "Arrhythmias" April 26, as part of the Panel Discussions and Clinical-Pathological Conferences.

PERRY S. MACNEAL, M.D., will preside at the Clinical Session at the Pennsylvania Hospital April 26. On April 28, DR. MACNEAL will speak on "Case Presentations of Uncommon Metabolic Diseases," at Pennsylvania Hospital, at a session of which he is also presiding officer.

MAX MILLER, M.D., will speak on "Fructose Metabolism in Diabetes" April 27, at Convention Hall.

WALDO E. NELSON, M.D., will participate in a conference on "What's New in Pediatrics" April 29 as part of the Panel Discussions and Clinical-Pathological Conferences. On the same morning, FERDINAND FETTER, M.D., will participate in a conference on "The Internist as a Marriage Counselor." DR. FETTER will also preside at a Clinical Session at the Presbyterian Hospital April 26, on "Group Therapy Session on Alcoholism," and "Late Results of Cardiac Surgery."

MICHAEL G. WOHL, M.D., will speak on "Nutrition in Congestive Heart Failure," at Philadelphia General Hospital April 26. DR. WOHL will also speak April 28 at Albert Einstein Medical Center on "Metabolic Bone

Disease with Special Emphasis on Post-Menopausal Osteoporosis." At this same clinical session, NORMAN G. SCHNEEBERG, M.D., will follow DR. WOHL with "Cyclic Nature of Thyrotoxicosis. Problems in Diagnosis."

Obituaries

KARL K. HERZ, M.D., of Hornell, New York, died in December 1954, at the age of 63. Dr. Herz, whose practice was limited to Internal Medicine, was Attending Physician at St. James Mercy, and Bethesda Hospitals. He had been an active member of the American Diabetes Association since 1946, and was a member of the American Medical Association and the American Heart Association. Dr. Herz graduated from the University of Göttingen, Germany, in 1920. He was awarded the Iron Cross for his services as a medical officer in the German Army in World War I.

MARGARET E. HILL, dietitian at St. Joseph Hospital in Orange, California, died Sept. 7, 1954, at the age of 28. Miss Hill received the degree of Bachelor of Science in Home Economics from the College of St. Elizabeth, Convent Station, N. J., and served a Dietetic Internship at St. Mary's Hospital, Rochester, Minnesota. She was a member of the Southern California and the American Dietetic Associations. Miss Hill was elected an Associate Member of the American Diabetes Association Sept. 1, 1954.

ELLIOTT FRANCIS MAGUIRE, M.D., died in Philadelphia on July 18, 1954.

Born in Philadelphia on April 16, 1915, he graduated from the University of Pennsylvania in 1939 with the degree of Bachelor of Arts and in 1943 received his M.D. degree from the University of Pennsylvania School of Medicine. After an internship at the Pennsylvania Hospital, Dr. Maguire became resident in pathology at the Abington (Pa.) Memorial Hospital during 1944-45 and was a Fellow in Medicine at the Lahey Clinic, Boston, during 1947-48. He joined the faculty of the University of Pennsylvania School of Medicine in 1949 as Assistant Instructor and, at the time of his death, was Instructor in Medicine. He had been a member of the staff of the Pennsylvania Hospital since 1948 and was Associate Physician and Assistant to the Medical Director of the Hospital's Benjamin Franklin Clinic.

Dr. Maguire was a diplomate of the American Board of Internal Medicine. He joined the American Diabetes Association in 1948. He was also a member of the American Medical Association, and the World Medical Association. He was elected as Associate of the American College of Physicians in 1950.

NATHAN D. WILENSKY, M.D., Brooklyn, New York, died Aug. 30, 1954, at the age of 46. Dr. Wilensky, whose practice was limited to internal medicine, was Assistant Physician at Maimonides Hospital, Attending Physician in charge of Peripheral Vascular Disease at the Jewish Chronic Disease Hospital, and Attending Physician at Kings County Hospital. He collaborated with William S. Collens, M.D., on the book, *Diagnosis and Treatment of Peripheral Vascular Diseases*. He graduated from New York Homeopathic Medical College and Flower Hospital in 1931. He joined the American Diabetes Association in 1946 and was a Founding Fellow of the Clinical Society of the New York Diabetes Association. He was also a member of the Peripheral Vascular Section of the American Heart Association. He is survived by his widow and two children.